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(54) Title: METHODS OF PREVENTING OR TREATING RECURRENCE OF MYOCARDIAL INFARCTION

(57) Abstract: Linkage of myocardial infarction (MI) with a locus on chromosome 12q23 is disclosed. In particular, the LTA4H gene within this locus is shown by association analysis to be a susceptibility gene for MI. Methods for preventing and/or treating the recurrence of MI, in particular are described.

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METHODS OF PREVENTING OR TREATING RECURRENCE OF MYOCARDIAL INFARCTION

RELATED APPLICATION

This application claims the benefit of U.S. Provisional Application No. 60/503,587, filed on September 17, 2003. The entire teachings of the above application are incorporated herein by reference.

BACKGROUND OF THE INVENTION

Myocardial Infarction (MI) is one of the most common diagnoses in hospitalized patients in industrialized countries. Myocardial Infarction generally occurs when there is an abrupt decrease in coronary blood flow following a thrombotic occlusion of a coronary artery previously narrowed by atherosclerosis. Infarction occurs when a coronary artery thrombus develops rapidly at a site of vascular injury, which is produced or facilitated by factors such as cigarette smoking, hypertension and lipid accumulation. In most cases, infarction occurs when an atherosclerotic plaque fissures, ruptures or ulcerates and when conditions favor thrombogenesis. In rare cases, infarction may be due to coronary artery occlusion caused by coronary emboli, congenital abnormalities, coronary spasm, and a wide variety of systemic, particularly inflammatory diseases.

Although classical risk factors such as smoking, hyperlipidemia, hypertension, and diabetes are associated with many cases of coronary heart disease (CHD) and MI, many patients do not have involvement of these risk factors. In fact, many patients who exhibit one or more of these risk factors do not develop MI. Family history has long been recognized as one of the major risk factors. Although some of the familial

clustering of MI reflects the genetic contribution to the other conventional risk factors, a large number of studies have suggested that there are significant genetic susceptibility factors, beyond those of the known risk factors (Friedlander Y, *et al., Br Heart J.* 1985; 53:382-7, Shea S. *et al., J. Am. Coll. Cardiol.* 1984; 4:793-801, and Hopkins P.N., *et al., Am. J. Cardiol.* 1988; 62:703-7). Major genetic susceptibility factors have not yet been published. Currently anti-coagulants (*e.g.*, aspirin) or cholesterol lowering drugs (*e.g.*, statins) are used to prevent or treat the recurrence of myocardial infarction.

SUMMARY OF THE INVENTION

As described herein, a gene on chromosome 12q23 has been identified as playing a major role in myocardial infarction (MI). The gene comprises nucleic acid that encodes leukotriene A4 hydrolase, herein after referred to as LTA4H.

The invention pertains to methods of treatment (prophylactic and/or therapeutic) for certain diseases and conditions (*e.g.*, MI, ACS, atherosclerosis) associated with LTA4H or with other members of the leukotriene pathway (*e.g.*, biosynthetic enzymes, such as 5- lipoxygenase activating protein (FLAP) and arachidonate 5-lipoxygenase (5-LO); catabolic enzymes, such as leukotriene B4 12-hydroxydehydrogenase (LTB4DH) and leukotriene B4 omega hydroxylase; receptors, modulators and/or binding agents of the enzymes; and receptors for leukotriene B4 (LTB4), including leukotriene B4 receptor 1 (BLT1), and leukotriene B4 receptor 2 (BLT2)). The methods include the following: methods of treatment for myocardial infarction or susceptibility to myocardial infarction; for acute coronary syndrome (ACS), *e.g.*, unstable angina, non-ST-elevation myocardial infarction (NSTEMI) or ST-elevation myocardial infarction (STEMI); for decreasing risk of a second myocardial infarction; for atherosclerosis, such as for patients requiring treatment (*e.g.*, angioplasty, stents, coronary artery bypass graft) to restore blood flow in arteries (*e.g.*, coronary arteries); and/or for decreasing leukotriene synthesis (*e.g.*, for preventing or treating recurrence of myocardial infarction).

In the methods of the invention, a leukotriene synthesis inhibitor is administered to an individual in a therapeutically effective amount. The leukotriene synthesis inhibitor can be an agent that inhibits or antagonizes a member of the leukotriene synthesis pathway (*e.g.*, LTA4H, FLAP, or 5-LO). For example, the leukotriene synthesis inhibitor can be an agent that inhibits or antagonizes LTA4H polypeptide activity (*e.g.*, an LTA4H inhibitor) and/or LTA4H nucleic acid expression, as described herein. In another embodiment, the leukotriene synthesis inhibitor is an agent that inhibits or antagonizes polypeptide activity and/or nucleic acid expression of another member of the leukotriene biosynthetic pathway (*e.g.*, FLAP, 5-LO) or an LTB4 receptor (*e.g.*, BLT1 and/or BLT2). In preferred embodiments, the agent alters activity and/or nucleic acid expression of LTA4H. Preferred agents include those set forth in the Agent Table and in the Additional LTA4H Agent List herein. In another embodiment, preferred agents can be: ethyl-1-[2-[4-(phenylmethyl)phenoxy]ethyl]-4-piperidine-carboxylate, otherwise known as SC-56938; [4-[5-(3-Phenyl-propyl)thiophen-2-yl]butoxy]acetic acid, otherwise known as RP64966; (R)-S-[[4-(dimethylamino)phenyl]methyl]-N-(3-mercapto-2methyl-1-oxopropyl-L-cycteine, otherwise known as SA6541; optically pure enantiomers, salts, chemical derivatives, and analogues. In another embodiment, the agent alters metabolism or activity of a leukotriene (*e.g.*, LTB4), such as leukotriene antagonists or antibodies to leukotrienes, as well as agents which alter activity of a leukotriene receptor (*e.g.*, BLT1 and/or BLT2).

In certain embodiments of the invention, the individual is an individual who has at least one risk factor, such as an at-risk haplotype for myocardial infarction; an at-risk haplotype in the LTA4H gene; a polymorphism in a LTA4H nucleic acid; an at-risk polymorphism in the FLAP gene, an at-risk polymorphism in the 5-LO gene promoter, diabetes; hypertension; hypercholesterolemia; elevated lp(a); obesity; a past or current smoker; an elevated inflammatory marker (*e.g.*, a marker such as C-reactive protein (CRP), serum amyloid A, myeloperoxidase (MPO), N-tyrosine, di-tyrosine, lipoprotein phospholipase A2 (Lp-PLA2), fibrinogen, a leukotriene, a leukotriene metabolite, interleukin-6, tissue necrosis factor-alpha, a soluble vascular cell adhesion molecule (sVCAM), a soluble intervascular adhesion molecule (sICAM), E-selectin,

matrix metalloprotease type-1, matrix metalloprotease type-2, matrix metalloprotease type-3, and matrix metalloprotease type-9); increased total cholesterol, LDL cholesterol and/or decreased HDL cholesterol; increased leukotriene synthesis; and/or at least one previous myocardial infarction, ACS, stable angina, atherosclerosis, history of peripheral arterial occlusive disease, previous or acute stroke or transient ischemic attack, and past or acute treatment for restoration of coronary artery blood flow (*e.g.*, angioplasty, stenting, coronary artery bypass graft).

The invention pertains to use of leukotriene synthesis inhibitors for the manufacture of a medicament for the prevention and/or treatment of MI, ACS, and/or atherosclerosis, as described herein, as well as for the manufacture of a medicament for the reduction of leukotriene synthesis.

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. 1 shows the results of the first step of the linkage analysis: multipoint non-parametric LOD scores for a framework marker map on chromosome 12. A LOD score suggestive of linkage of 1.95 was found at marker D12S2081.

FIG. 2 shows the results of the second step of the linkage analysis: multipoint non-parametric LOD scores for the families after adding 20 fine mapping markers to the candidate region. The inclusion of additional microsatellite markers increased the information on sharing by decent from 0.8 to 0.9, around the markers that gave the highest LOD scores.

FIGS. 3.1-3.33 show the genomic sequence of the LTA4H gene (SEQ ID NO: 1).

FIG. 4 shows the sequence of the LTA4H mRNA (SEQ ID NO: 2).

FIG. 5 shows the sequence of the LTA4H polypeptide (SEQ ID NO: 3).

FIGS. 6.1-6.32 show the sequences of particular SNPs of the LTA4H gene (SEQ ID NOs: 4-92).

FIGS. 7.1-7.8 show the sequences of other particular SNPs of the LTA4H gene (SEQ ID NOs: 93-117).

DETAILED DESCRIPTION OF THE INVENTION

In a genome wide search for genes that cause MI using a large number of Icelandic patients and families, linkage (that is, excess sharing of a given location in the genome) was found to a locus or location on chromosome 12q23. Given our past discovery that FLAP is major gene contributing to MI risk, we noted that a candidate gene encoding a protein in the same molecular pathway as FLAP, LTA4H, resided within this locus. Three microsatellite markers and 12 SNPs spanning a 79kb region across the LTA4H gene were genotyped in approximately 1000 patients and 460 controls.

A haplotype consisting of 2 microsatellite markers and 2 SNPs was found to be in significant excess in MI patients, compared with controls. These results strongly suggest that the LTA4H gene is a susceptibility gene for myocardial infarction and is likely involved in its pathogenesis or underlying disease process. The LTA4H nucleic acid encodes an enzyme, leukotriene A4 hydrolase, which participates in leukotriene biosynthesis. Other members of the leukotriene pathway have been shown to be associated with MI (see U.S. Provisional Application No. 60/419,432, filed on October 17, 2002; U.S. Patent Application No. 10/829,674, filed on April 22, 2004). Mutations and/or polymorphisms within the LTA4H nucleic acid that show association with the disease can potentially be used for diagnostic purposes. Furthermore, the LTA4H gene, and other members of the leukotriene pathway are therapeutic targets for myocardial infarction.

The leukotrienes are a family of highly potent biological mediators of inflammatory processes produced primarily by bone marrow derived leukocytes such as monocytes, macrophages, and neutrophils. Leukotriene biosynthetic enzymes are detected within atherosclerosis lesions, indicating that the vessel itself can be a source of leukotrienes. Increased production of leukotrienes in individuals with pre-existing atherosclerosis lesions may lead to plaque instability or friability of the fibrous cap leading to local thrombotic events. If this occurs in coronary artery arteries it leads to MI or unstable angina. If it occurs in the cerebrovasculature it leads to stroke or transient ischemic attack. If it occurs in large arteries to the limbs, it causes or

exacerbates limb ischemia in persons with peripheral arterial occlusive disease (PAOD). Therefore, those with genetically influenced predisposition to produce higher leukotriene levels may be at higher risk for local thrombotic events over a pre-existing atherosclerosic lesion leading to ischemic events such as MI, stroke, and PAOD. In addition, local leukotriene production by cells within atherosclerotic plaques and the vasculature may accelerate the progression of atherosclerosis and increase the risk of clinically important atherosclerosis.

As a result of these discoveries, methods are now available for the prevention and/or treatment of myocardial infarction (MI) and acute coronary syndrome (ACS) through the use of leukotriene inhibitors, such as agents that inhibit leukotriene biosynthesis or antagonize signaling through leukotriene receptors. The term, "treatment" as used herein, refers not only to ameliorating symptoms associated with the disease or condition, but also preventing or delaying the onset of the disease or condition; preventing or delaying the occurrence of a second episode of the disease or condition; and/or also lessening the severity or frequency of symptoms of the disease or condition. In the case of atherosclerosis, "treatment" also refers to a minimization or reversal of the development of plaques. Methods are additionally available for assessing an individual's risk for MI or ACS. In preferred embodiment, the individual to be treated is an individual who is susceptible (at increased risk) for MI or ACS, such as an individual who is in one of the representative target populations described herein.

REPRESENTATIVE TARGET POPULATIONS

We have defined several target populations that may especially benefit from medicaments developed against LTA4H.

In one embodiment of the invention, an individual who is at risk for MI or ACS is an individual who has an at-risk haplotype in LTA4H, as described herein. In one embodiment, the haplotype can comprise alleles 0, T, 0, and A, of markers DG12S1664, SG12S26, DG12S1666, and SG12S144, respectively, at the 12q23 locus. This LTA4H "at-risk" haplotype is detected in over 76 % of male patients who

have previously had an MI, conferring an increased relative risk of 1.4 fold and in 72% of female MI patients with a relative risk of 1.2. Increased risk for MI or ACS in individuals with an LTA4H at-risk haplotype is logically conferred by increased production of leukotrienes in the arterial vessel wall or in bone-marrow derived inflammatory cells within the blood and/or arterial vessel wall. In another embodiment of the invention, an individual who is at risk for MI or ACS is an individual who has a polymorphism in an LTA4H gene, in which the presence of the polymorphism is indicative of a susceptibility to MI or ACS. The term "gene," as used herein, refers to not only the sequence of nucleic acids encoding a polypeptide, but also the promoter regions, transcription enhancement elements, splice donor/acceptor sites, and other non-transcribed nucleic acid elements. Representative polymorphisms include those presented in Table 3. Along the same lines, certain variants in the FLAP gene and other members of the leukotriene biosynthetic and response pathway (see, U.S. Provisional Application No. 60/419,432, filed on October 17, 2002; U.S. Patent Application No. 10/829,674, filed on April 22, 2004) may indicate one's increased risk for MI and ACS. Other representatibe at-risk haplotypes are shown in Table 4 and Table 5. Additional "at-risk" haplotypes can be determined using linkage disequilibrium and/or haplotype blocks, as described below.

In a further embodiment, an individual who is at risk for MI or ACS is an individual who has an elevated inflammatory marker. An "elevated inflammatory marker," as used herein, is the presence of an amount of an inflammatory marker that is greater, by an amount that is statistically significant, than the amount that is typically found in control individual(s) or by comparison of disease risk in a population associated with the lowest band of measurement (*e.g.*, below the mean or median, the lowest quartile or the lowest quintile) compared to higher bands of measurement (*e.g.*, above the mean or median, the second, third or fourth quartile; the second, third, fourth or fifth quintile). An "inflammatory marker" refers to a molecule that is indicative of the presence of inflammation in an individual, for example, C-reactive protein (CRP), serum amyloid A, myeloperoxidase (MPO), N-tyrosine, di-tyrosine, lipoprotein phospholipase A2 (Lp-PLA2), fibrinogen, leukotriene levels

(*e.g.*, LTB4, LTE4), leukotriene metabolites (*e.g.*, 12-oxo-LTB4, 10,11,14,15-tetrahydro-12-oxo-LTB4), interleukin-6, tissue necrosis factor-alpha, soluble vascular cell adhesion molecules (sVCAM), soluble intervascular adhesion molecules (sICAM), E-selectin, matrix metalloprotease type-1, matrix metalloprotease type-2, matrix metalloprotease type-3, and matrix metalloprotease type-9) or other markers (see, *e.g.*, Doggen, C.J.M. *et al., J.. Internal Med.*, *248*:406-414 (2000); Ridker, P.M. *et al., New Englnd. J. Med.* 1997: *336*: 973-979, Rettersol, L. *et al.,* 2002: *160*:433-440; Ridker, P.M. *et. al., New England. J. Med.*, 2002: *347*: 1557-1565; Bermudez, E.A. *et .al., Arterioscler. Thromb. Vasc. Biol.* , 2002: *22*:1668-1673). In certain embodiments, the presence of such inflammatory markers can be measured in serum or urine.

In a third embodiment, an individual who is at risk for MI or ACS is an individual who has increased total cholesterol, increased LDL cholesterol and/or decreased HDL cholesterol levels. For example, the American Heart Association indicates that an LDL cholesterol level of less than 100 mg/dL is optimal; from 100-129 mg/dL is near/above optimal; from 130-159 mg/dL is borderline high; from 160-189 is high; and from 190 and up is very high. Therefore, an individual who is at risk for MI or ACS because of an increased LDL cholesterol level is, for example, an individual who has more than 100 mg/dL cholesterol, such as an individual who has a near/above optimal level, a borderline high level, a high level or a very high level. Similarly, the American Heart Association indicates that an HDL cholesterol level of less than 40 mg/dL is a major risk factor for heart disease; and an HDL cholesterol level of 60 mg/dL or more is protective against heart disease. Thus, an individual who is at risk for MI or ACS because of a decreased HDL cholesterol level is, for example, an individual who has less than 60 mg/dL HDL cholesterol, such as an individual who has less than 40 mg/dL HDL cholesterol.

In a fourth embodiment, an individual who is at risk for MI or ACS is an individual who has increased leukotriene synthesis. "Increased leukotriene synthesis," as used herein, indicates an amount of production of leukotrienes that is greater, by an amount that is statistically significant, than the amount of production of leukotrienes

that is typically found in control individual(s) or by comparison of leukotriene production in a population associated with the lowest band of measurement (*e.g.*, below the mean or median, the lowest quartile or the lowest quintile) compared to higher bands of measurement (*e.g.*, above the mean or median, the second, third or fourth quartile; the second, third, fourth or fifth quintile). An individual can be assessed for the presence of increased leukotriene synthesis by a variety of methods. For example, an individual can be assessed for an increased risk of MI, ACS or atherosclerosis, by assessing the level of a leukotriene metabolite (*e.g.*, LTB4, LTE4) in a sample (*e.g.*, serum, plasma or urine) from the individual. An increased level of leukotriene metabolites is indicative of increased production of leukotrienes, and of an increased risk of MI, ACS or atherosclerosis.

In a further embodiment, an individual who is at risk for MI or ACS is an individual who has already experienced at least one MI or ACS event, or who has stable angina, and is therefore at risk for a second MI or ACS event. In another embodiment, an individual who is at risk for MI or ACS is an individual who has atherosclerosis or who requires treatment (*e.g.*, angioplasty, stenting, coronary artery bypass graft) to restore blood flow in arteries.

In additional embodiments, an individual who is at risk for MI or ACS is an individual who has diabetes; hypertension; hypercholesterolemia; elevated lp(a); obesity; acute or past stroke or transient ischemic event, peripheral arterial occlusive disease, and/or is a past or current smoker.

Individuals at risk for MI or ACS may fall into more than one of these representative target populations. For example, an individual may have experienced at least one MI or ACS event, and may also have an increased level of an inflammatory marker. As used therein, the term “individual in a target population” refers to an individual who is at risk for MI or ACS who falls into at least one of the representative target populations described above.

ASSESSMENT FOR AT-RISK HAPLOTYPES

A "haplotype," as described herein, refers to a combination of genetic markers ("alleles"). In a certain embodiment, the haplotype can comprise two or more alleles, three or more alleles, four or more alleles, or five or more alleles. The genetic markers are particular "alleles" at "polymorphic sites" associated with LTA4H. A nucleotide position at which more than one sequence is possible in a population (either a natural population or a synthetic population, *e.g.*, a library of synthetic molecules), is referred to herein as a "polymorphic site". Where a polymorphic site is a single nucleotide in length, the site is referred to as a single nucleotide polymorphism ("SNP"). For example, if at a particular chromosomal location, one member of a population has an adenine and another member of the population has a thymine at the same position, then this position is a polymorphic site, and, more specifically, the polymorphic site is a SNP. Polymorphic sites can allow for differences in sequences based on substitutions, insertions or deletions. Each version of the sequence with respect to the polymorphic site is referred to herein as an "allele" of the polymorphic site. Thus, in the previous example, the SNP allows for both an adenine allele and a thymine allele.

Typically, a reference sequence is referred to for a particular sequence. Alleles that differ from the reference are referred to as "variant" alleles. For example, the reference LTA4H sequence is described herein by SEQ ID NO:1. The term, "variant LTA4H", as used herein, refers to a sequence that differs from SEQ ID NO:1, but is otherwise substantially similar. The genetic markers that make up the haplotypes described herein are LTA4H variants.

Additional variants can include changes that affect a polypeptide, *e.g.*, the LTA4H polypeptide. These sequence differences, when compared to a reference nucleotide sequence, can include the insertion or deletion of a single nucleotide, or of more than one nucleotide, resulting in a frame shift; the change of at least one nucleotide, resulting in a change in the encoded amino acid; the change of at least one nucleotide, resulting in the generation of a premature stop codon; the deletion of several nucleotides, resulting in a deletion of one or more amino acids encoded by the

nucleotides; the insertion of one or several nucleotides, such as by unequal recombination or gene conversion, resulting in an interruption of the coding sequence of a reading frame; duplication of all or a part of a sequence; transposition; or a rearrangement of a nucleotide sequence, as described in detail above. Such sequence changes alter the polypeptide encoded by an LTA4H nucleic acid. For example, if the change in the nucleic acid sequence causes a frame shift, the frame shift can result in a change in the encoded amino acids, and/or can result in the generation of a premature stop codon, causing generation of a truncated polypeptide. Alternatively, a polymorphism associated with MI or a susceptibility to MI can be a synonymous change in one or more nucleotides (*i.e.*, a change that does not result in a change in the amino acid sequence). Such a polymorphism can, for example, alter splice sites, affect the stability or transport of mRNA, or otherwise affect the transcription or translation of the polypeptide. The polypeptide encoded by the reference nucleotide sequence is the "reference" polypeptide with a particular reference amino acid sequence, and polypeptides encoded by variant alleles are referred to as "variant" polypeptides with variant amino acid sequences.

In one embodiment, haplotypes can be used to identify individuals at risk for MI OR ACS. Haplotypes are a combination of genetic markers, *e.g.*, particular alleles at polymorphic sites. Markers can include, for example, SNPs and microsatellites. The haplotypes can comprise a combination of various genetic markers; therefore, detecting haplotypes can be accomplished by methods known in the art for detecting sequences at polymorphic sites. For example, standard techniques for genotyping for the presence of SNPs and/or microsatellite markers can be used, such as fluorescent based techniques (Chen, *et al.*, *Genome Res.* *9*, 492 (1999)), PCR, LCR, Nested PCR and other techniques for nucleic acid amplification. These markers and SNPs can be identified in at-risk haploptypes. Certain methods of identifying relevant markers and SNPs include the use of linkage disequilibrium (LD) and/or LOD scores.

Linkage Disequilibrium

Linkage Disequilibrium (LD) refers to a non-random assortment of two genetic elements. For example, if a particular genetic element (*e.g.*, "alleles" at a polymorphic site) occurs in a population at a frequency of 0.25 and another occurs at a frequency of 0.25, then the predicted occurrance of a person's having both elements is 0.125, assuming a random distribution of the elements. However, if it is discovered that the two elements occur together at a frequency higher than 0.125, then the elements are said to be in linkage disequilibrium since they tend to be inherited together at a higher rate than what their independent allele frequencies would predict. Roughly speaking, LD is generally correlated with the frequency of recombination events between the two elements.

Many different measures have been proposed for assessing the strength of linkage disequilibrium (LD). Most capture the strength of association between pairs of biallelic sites. Two important pairwise measures of LD are r^2 (sometimes denoted ^{2}) and $|D'|$. Both measures range from 0 (no disequilibrium) to 1 ('complete' disequilibrium), but their interpretation is slightly different. $|D'|$ is defined in such a way that it is equal to 1 if just two or three of the possible haplotypes are present, and it is <1 if all four possible haplotypes are present. So, a value of $|D'|$ that is <1 indicates that historical recombination has occurred between two sites (recurrent mutation can also cause $|D'|$ to be <1, but for single nucleotide polymorphisms (SNPs) this is usually regarded as being less likely than recombination). The measure r^2 represents the statistical correlation between two sites, and takes the value of 1 if only two haplotypes are present. It is arguably the most relevant measure for association mapping, because there is a simple inverse relationship between r^2 and the sample size required to detect association between susceptibility loci and SNPs. These measures are defined for pairs of sites, but for some applications a determination of how strong LD is across an entire region that contains many polymorphic sites might be desirable (*e.g.*, testing whether the strength of LD differs significantly among loci or across populations, or whether there is more or less LD in a region than predicted under a

particular model). Measuring LD across a region is not straightforward, but one approach is to use the measure r, which was developed in population genetics. Roughly speaking, r measures how much recombination would be required under a particular population model to generate the LD that is seen in the data. This type of method can potentially also provide a statistically rigorous approach to the problem of determining whether LD data provide evidence for the presence of recombination hotspots.

Haplotypes and LOD Score Definition of a Susceptibility Locus

In certain embodiments, haplotype analysis involves defining a candidate susceptibility locus using LOD scores. The defined regions are then ultra-fine mapped with microsatellite markers with an average spacing between markers of less than 100 kb. All usable microsatellite markers that are found in public databases and mapped within that region can be used. In addition, microsatellite markers identified within the deCODE genetics sequence assembly of the human genome can be used. The frequencies of haplotypes in the patient and the control groups can be estimated using an expectation-maximization algorithm (Dempster A. *et al.*, 1977. *J. R. Stat. Soc. B*, 39:1-389). An implementation of this algorithm that can handle missing genotypes and uncertainty with the phase can be used. Under the null hypothesis, the patients and the controls are assumed to have identical frequencies. Using a likelihood approach, an alternative hypothesis is tested, where a candidate at-risk-haplotype, which can include the markers described herein, is allowed to have a higher frequency in patients than controls, while the ratios of the frequencies of other haplotypes are assumed to be the same in both groups. Likelihoods are maximized separately under both hypotheses and a corresponding 1-df likelihood ratio statistic is used to evaluate the statistic significance.

To look for at-risk-haplotypes in the 1-lod drop, for example, association of all possible combinations of genotyped markers is studied, provided those markers span a practical region. The combined patient and control groups can be randomly divided into two sets, equal in size to the original group of patients and controls. The

haplotype analysis is then repeated and the most significant p-value registered is determined. This randomization scheme can be repeated, for example, over 100 times to construct an empirical distribution of p-values. In a preferred embodiment, a p-value of <0.05 is indicative of an at-risk haplotype.

A detailed discussion of haplotype analysis follows.

Haplotype analysis

One general approach to haplotype analysis involves using likelihood-based inference applied to NEsted MOdels. The method is implemented in the program NEMO, which allows for many polymorphic markers,. SNPs and microsatellites. The method and software are specifically designed for case-control studies where the purpose is to identify haplotype groups that confer different risks. It is also a tool for studying LD structures.

When investigating haplotypes constructed from many markers, apart from looking at each haplotype individually, meaningful summaries often require putting haplotypes into groups. A particular partition of the haplotype space is a model that assumes haplotypes within a group have the same risk, while haplotypes in different groups can have different risks. Two models/partitions are nested when one, the alternative model, is a finer partition compared to the other, the null model, *i.e,* the alternative model allows some haplotypes assumed to have the same risk in the null model to have different risks. The models are nested in the classical sense that the null model is a special case of the alternative model. Hence traditional generalized likelihood ratio tests can be used to test the null model against the alternative model. Note that, with a multiplicative model, if haplotypes h_i and h_j are assumed to have the same risk, it corresponds to assuming that $f_i \; p_i = f_j \; p_j$ where f and p denote haplotype frequencies in the affected population and the control population respectively.

One common way to handle uncertainty in phase and missing genotypes is a two-step method of first estimating haplotype counts and then treating the estimated counts as the exact counts, a method that can sometimes be problematic (*e.g.,* see the information measure section below) and may require randomization to properly

evaluate statistical significance. In NEMO, maximum likelihood estimates, likelihood ratios and p-values are calculated directly, with the aid of the EM algorithm, for the observed data treating it as a missing-data problem.

NEMO allows complete flexibility for partitions. For example, the first haplotype problem described in the Methods section on Statistical analysis considers testing whether h_1 has the same risk as the other haplotypes $h_2, \ldots, h_k$. Here the alternative grouping is $[h_1], [h_2, \ldots, h_k]$ and the null grouping is $[h_1, \ldots, h_k]$. The second haplotype problem in the same section involves three haplotypes h_1 = G0, h_2 = GX and h_3 = AX, and the focus is on comparing h_1 and h_2. The alternative grouping is $[h_1], [h_2], [h_3]$ and the null grouping is $[h_1, h_2], [h_3]$. If composite alleles exist, one could collapse these alleles into one at the data processing stage, and performed the test as described. This is a perfectly valid approach, and indeed, whether we collapse or not makes no difference if there were no missing information regarding phase. But, with the actual data, if each of the alleles making up a composite correlates differently with the SNP alleles, this will provide some partial information on phase. Collapsing at the data processing stage will unnecessarily increase the amount of missing information. A nested-models/partition framework can be used in this scenario. Let h_2 be split into $h_{2a}, h_{2b}, \ldots, h_{2e}$, and h_3 be split into $h_{3a}, h_{3b}, \ldots, h_{3e}$. Then the alternative grouping is $[h_1], [h_{2a}, h_{2b}, \ldots, h_{2e}], [h_{3a}, h_{3b}, \ldots, h_{3e}]$ and the null grouping is $[h_1, h_{2a}, h_{2b}, \ldots, h_{2e}], [h_{3a}, h_{3b}, \ldots, h_{3e}]$. The same method can be used to handle composite where collapsing at the data processing stage is not even an option since L_C represents multiple haplotypes constructed from multiple SNPs. Alternatively, a 3-way test with the alternative grouping of $[h_1], [h_{2a}, h_{2b}, \ldots, h_{2e}], [h_{3a}, h_{3b}, \ldots, h_{3e}]$ versus the null grouping of $[h_1, h_{2a}, h_{2b}, \ldots, h_{2e}, h_{3a}, h_{3b}, \ldots, h_{3e}]$ could also be performed. Note that the generalized likelihood ratio test-statistic would have two degrees of freedom instead of one.

Measuring information

Even though likelihood ratio tests based on likelihoods computed directly for the observed data, which have captured the information loss due to uncertainty in phase and missing genotypes, can be relied on to give valid p-values, it would still be

of interest to know how much information had been lost due to the information being incomplete. Interestingly, one can measure information loss by considering a two-step procedure to evaluating statistical significance that appears natural but happens to be systematically anti-conservative. Suppose we calculate the maximum likelihood estimates for the population haplotype frequencies calculated under the alternative hypothesis that there are differences between the affected population and control population, and use these frequency estimates as estimates of the observed frequencies of haplotype counts in the affected sample and in the control sample. Suppose we then perform a likelihood ratio test treating these estimated haplotype counts as though they are the actual counts. We could also perform a Fisher's exact test, but we would then need to round off these estimated counts since they are in general non-integers. This test will in general be anti-conservative because treating the estimated counts as if they were exact counts ignores the uncertainty with the counts, overestimates the effective sample size and underestimates the sampling variation. It means that the chi-square likelihood-ratio test statistic calculated this way, denoted by Λ^*, will in general be bigger than Λ, the likelihood-ratio test-statistic calculated directly from the observed data as described in methods. But Λ^* is useful because the ratio Λ/Λ^* happens to be a good measure of information, or $1 - (\Lambda/\Lambda^*)$ is a measure of the fraction of information lost due to missing information. This information measure for haplotype analysis is described in Nicolae and Kong, Technical Report 537, Department of Statistics, University of Statistics, University of Chicago, Revised for *Biometrics* (2003) as a natural extension of information measures defined for linkage analysis, and is implemented in NEMO.

Statistical analysis

For single marker association to the disease, the Fisher exact test can be used to calculate two-sided p-values for each individual allele. All p-values are presented unadjusted for multiple comparisons unless specifically indicated. The presented frequencies (for microsatellites, SNPs and haplotypes) are allelic frequencies as opposed to carrier frequencies. To minimize any bias due the relatedness of the patients who were recruited as families for the linkage analysis, first and second-

degree relatives can be eliminated from the patient list. Furthermore, the test can be repeated for association correcting for any remaining relatedness among the patients, by extending a variance adjustment procedure (*e.g.*, as described in Risch, N. & Teng, J., "The relative power of family-based and case-control designs for linkage disequilibrium studies of complex human diseases I. DNA pooling," *Genome Res.* 8:1278-1288 (1998)) for sibships so that it can be applied to general familial relationships, and present both adjusted and unadjusted p-values for comparison. The differences are in general very small as expected. To assess the significance of single-marker association corrected for multiple testing we carried out a randomisation test using the same genotype data. Cohorts of patients and controls can be randomized and the association analysis redone multiple times (e.g., up to 500,000 times) and the p-value is the fraction of replications that produced a p-value for some marker allele that is lower than or equal to the p-value we observed using the original patient and control cohorts.

For both single-marker and haplotype analyses, relative risk (RR) and the population attributable risk (PAR) can be calculated assuming a multiplicative model (haplotype relative risk model), (Terwilliger, J.D. & Ott, J., *Hum Hered,* 42, 337-46 (1992) and Falk, C.T. & Rubinstein, P, *Ann Hum Genet* 51 (Pt 3), 227-33 (1987)), i.e., that the risks of the two alleles/haplotypes a person carries multiply. For example, if RR is the risk of A relative to a, then the risk of a person homozygote AA will be RR times that of a heterozygote Aa and RR^2 times that of a homozygote aa. The multiplicative model has a nice property that simplifies analysis and computations - haplotypes are independent, *i.e.,* in Hardy-Weinberg equilibrium, within the affected population as well as within the control population. As a consequence, haplotype counts of the affecteds and controls each have multinomial distributions, but with different haplotype frequencies under the alternative hypothesis. Specifically, for two haplotypes h_i and h_j, $\mathrm{risk}(h_i)/\mathrm{risk}(h_j) = (f_i/p_i)/(f_j/p_j)$, where f and p denote respectively frequencies in the affected population and in the control population. While there is some power loss if the true model is not

multiplicative, the loss tends to be mild except for extreme cases. Most importantly, p-values are always valid since they are computed with respect to null hypothesis.

In general, haplotype frequencies are estimated by maximum likelihood and tests of differences between cases and controls are performed using a generalized likelihood ratio test (Rice, J.A. *Mathematical Statistics and Data Analysis*, 602 (International Thomson Publishing, (1995)). deCODE's haplotype analysis program called NEMO, which stands for NEsted MOdels, can be used to calculate all the haplotype results. To handle uncertainties with phase and missing genotypes, it is emphasized that we do not use a common two-step approach to association tests, where haplotype counts are first estimated, possibly with the use of the EM algorithm, Dempster, (A.P., Laird, N.M. & Rubin, D.B., *Journal of the Royal Statistical Society B,* 39, 1-38 (1971)) and then tests are performed treating the estimated counts as though they are true counts, a method that can sometimes be problematic and may require randomisation to properly evaluate statistical significance. Instead, with NEMO, maximum likelihood estimates, likelihood ratios and p-values are computed with the aid of the EM-algorithm directly for the observed data, and hence the loss of information due to uncertainty with phase and missing genotypes is automatically captured by the likelihood ratios. Even so, it is of interest to know how much information is retained, or lost, due to incomplete information. Described herein is such a measure that is natural under the likelihood framework. For a fixed set of markers, the simplest tests performed compare one selected haplotype against all the others. Call the selected haplotype h_1 and the others $h_2, \ldots, h_k$. Let $p_1, \ldots, p_k$ denote the population frequencies of the haplotypes in the controls, and $f_1, \ldots, f_k$ denote the population frequencies of the haplotypes in the affecteds. Under the null hypothesis, $f_i = p_i$ for all i. The alternative model we use for the test assumes $h_2, \ldots, h_k$ to have the same risk while h_1 is allowed to have a different risk. This implies that while p_1 can be different from f_1, f_i $(f_2+\ldots+f_k) = p_i$ $(p_2+\ldots+p_k) = \beta_i$ for $i = 2, \ldots, k$. Denoting f_1 p_1 by r, and noting that $\beta_2+\ldots+\beta_k = 1$, the test statistic based on generalized likelihood ratios is

$$\Lambda = 2\left[\ell(\hat{r},\hat{p}_1,\hat{\beta}_2,...,\hat{\beta}_{k-1}) - \ell(1,\tilde{p}_1,\tilde{\beta}_2,...,\tilde{\beta}_{k-1})\right]$$

where ℓ denotes $\log_e$likelihood and ˜ and ^ denote maximum likelihood estimates under the null hypothesis and alternative hypothesis respectively. Λ has asymptotically a chi-square distribution with 1-df, under the null hypothesis. Slightly more complicated null and alternative hypotheses can also be used. For example, let h_1 be G0, h_2 be GX and h_3 be AX. When comparing G0 against GX, *i.e.*, this is the test which gives estimated RR of 1.46 and p-value = 0.0002, the null assumes G0 and GX have the same risk but AX is allowed to have a different risk. The alternative hypothesis allows, for example, three haplotype groups to have different risks. This implies that, under the null hypothesis, there is a constraint that $f_1\ p_1 = f_2\ p_2$, or $w = [f_1\ p_1]\ \ [f_2\ p_2] = 1$. The test statistic based on generalized likelihood ratios is

$$\Lambda = 2\left[\ell(\hat{p}_1,\hat{f}_1,\hat{p}_2,\hat{w}) - \ell(\tilde{p}_1,\tilde{f}_1,\tilde{p}_2,1)\right]$$

that again has asymptotically a chi-square distribution with 1-df under the null hypothesis. If there are composite haplotypes (for example, h_2 and h_3), that is handled in a natural manner under the nested models framework.

Linkage Disequilibrium using NEMO

LD between pairs of SNPs can also be calculated using the standard definition of D' and R^2 (Lewontin, R., Genetics 49, 49-67 (1964) and Hill, W.G. & Robertson, A. Theor. Appl. Genet. 22, 226-231 (1968)). Using NEMO, frequencies of the two marker allele combinations are estimated by maximum likelihood and deviation from linkage equilibrium is evaluated by a likelihood ratio test. The definitions of D' and R^2 are extended to include microsatellites by averaging over the values for all possible allele combination of the two markers weighted by the marginal allele probabilities. When plotting all marker combination to elucidate the LD structure in a particular region, we plot D' in the upper left corner and the p-value in the lower right corner. In the LD plots the markers can be plotted equidistant rather than according to their physical location, if desired.

Statistical Methods for Linkage Analysis

Multipoint, affected-only allele-sharing methods can be used in the analyses to assess evidence for linkage. Results, both the LOD-score and the non-parametric linkage (NPL) score, can be obtained using the program Allegro (Gudbjartsson *et al., Nat. Genet. 25:*12-3, 2000). Our baseline linkage analysis uses the Spairs scoring function (Whittemore, A.S., Halpern, J. (1994), *Biometrics 50*:118-27; Kruglyak L, *et al.* (1996), *Am J Hum Genet 58*:1347-63), the exponential allele-sharing model (Kong, A. and Cox, N.J. (1997), *Am J Hum Genet 61*:1179-88) and a family weighting scheme that is halfway, on the log-scale, between weighting each affected pair equally and weighting each family equally. The information measure we use is part of the Allegro program output and the information value equals zero if the marker genotypes are completely uninformative and equals one if the genotypes determine the exact amount of allele sharing by decent among the affected relatives (Gretarsdottir *et al., Am. J. Hom. Genet, 70*:593-603, (2002)). We computed the P-values two different ways and here report the less significant result. The first P-value can be computed on the basis of large sample theory; the distribution of Z_{lr} = ($2[\log_e(10)\text{LOD}]$) approximates a standard normal variable under the null hypothesis of no linkage (Kong, A. and Cox, N.J. (1997), *Am J Hum Genet 61*:1179-88). The second P-value can be calculated by comparing the observed LOD-score with its complete data sampling distribution under the null hypothesis (e.g., Gudbjartsson *et al., Nat. Genet. 25:*12-3, 2000). When the data consist of more than a few families, these two P-values tend to be very similar.

Haplotypes and "Haplotype Block" Definition of a Susceptibility Locus

In certain embodiments, haplotype analysis involves defining a candidate susceptibility locus based on "haplotype blocks." It has been reported that portions of the human genome can be broken into series of discrete haplotype blocks containing a few common haplotypes; for these blocks, linkage disequilibrium data provided little evidence indicating recombination (see, e.g., Wall., J.D. and Pritchard, J.K., *Nature Reviews Genetics* 4: 587-597 (2003); Daly, M. *et al., Nature Genet.* 29:229-232

(2001); Gabriel, S.B. *et al., Science* 296:2225-2229 (2002); Patil, N. *et al., Science* 294:1719-1723 (2001); Dawson, E. *et al., Nature* 418:544-548 (2002); Phillips, M.S. *et al., Nature Genet.* 33:382-387 (2003)).

There are two main methods for defining haplotype blocks: blocks can be defined as regions of DNA that have limited haplotype diversity (see, e.g., Daly, M. *et al., Nature Genet.* 29:229-232 (2001); Patil, N. *et al., Science* 294:1719-1723 (2001); Dawson, E. *et al., Nature* 418:544-548 (2002); Zhang, K. *et al., PNAS SA* 99:7335-7339 (2002)), or as regions between transition zones having extensive historical recombination, identified using linkage disequilibrium (see, e.g., Gabriel, S.B. *et al., Science* 296:2225-2229 (2002);Phillips, M.S. *et al., Nature Genet.* 33:382-387 (2003); Wang, N. *et al., Am. J. Hum. Genet.* 71:1227-1234 (2002); Stumpf, M.P., and Goldstein, D.B., *Curr. Biol.* 13:1-8 (2003)). As used herein, the term, "haplotype block" includes blocks defined by either characteristic.

Representative methods for identification of haplotype blocks are set forth, for example, in U.S. Published Patent Applications 20030099964; 20030170665; 20040023237; 20040146870. Haplotype blocks can be used readily to map associations between phenotype and haplotype status. The main haplotytpes can be identified in each haplotype block, and then a set of "tagging" SNPs or markers (the smallest set of SNPs or markers needed to distinguish among the haplotypes) can then be identified These tagging SNPs or markers can then be used in assessment of samples from groups of individuals, in order to identify association between phenotype and haplotype. If desired, neighboring haplotype blocks can be assessed concurrently, as there may also exist linkage disequilibrium among the haplotype blocks.

Haplotypes and Diagnostics

Certain haplotypes as described herein, *e.g.*, having markers such as those shown in Table 3, 4 or 5, have been found more frequently in individuals with MI and/or ACS than in individuals without MI and/or ACS. Therefore, these "at-risk" haplotypes have predictive value for detecting a susceptibility to MI or ACS in an

individual. In addition, haplotype blocks comprising certain tagging markers, can be found more frequently in individuals with MI or ACS than in individuals without MI or ACS. Therefore, these "at-risk" tagging markers within the haplotype blocks also have predictive value for detecting a susceptibility to MI or ACS in an individual. "At-risk" tagging markers within the haplotype blocks can also include other markers that distinguish among the haplotypes, as these similarly have predictive value for detecting a susceptibility to MI or ACS in an individual.

The haplotypes and tagging markers useful herein are in some cases a combination of various genetic markers, *e.g.*, SNPs and microsatellites. Therefore, detecting haplotypes can be accomplished by methods known in the art for detecting sequences at polymorphic sites, such as the methods described above. Furthermore, correlation between certain haplotypes or sets of tagging markers and disease phenotype can be verified using standard techniques. A representative example of a simple test for correlation would be a Fisher-exact test on a two by two table.

In specific embodiments, an at-risk haplotype in, or comprising portions of, the LTA4H gene, is one where the haplotype is more frequently present in an individual at risk for MI or ACS (affected), compared to the frequency of its presence in a healthy individual (control), and wherein the presence of the haplotype is indicative of susceptibility to MI or ACS. In other embodiments, at-risk tagging markers in a haplotype block in linkage disequilibrium with one or more markers in the LTA4H gene, are tagging markers which are more frequently present in an individual at risk for MI or ACS (affected), compared to the frequency of their presence in a healthy individual (control), and wherein the presence of the tagging markers is indicative of susceptibility to MI or ACS. In a further embodiments, at-risk markers in linkage disequilibrium with one or more markers in the LTA4H gene, are markers which are more frequently present in an individual at risk for MI or ACS (affected), compared to the frequency of their presence in a healthy individual (control), and wherein the presence of the markers is indicative of susceptibility to MI or ACS. In particularly preferred embodiments of the invention, at-risk haplotypes include haplotypes as shown in Table 4 or Table 5.

In certain methods described herein, an individual who is at risk for MI or ACS is an individual in whom an at-risk haplotype is identified, or an individual in whom at-risk tagging markers are identified. In one embodiment, the at-risk haplotype or at-risk tagging markers confer a significant risk of MI or ACS. In one embodiment, significant risk of MI or ACS is measured by an odds ratio; in another embodiment, significant risk is measured by a percentage. In one embodiment, a significant risk is measured as an odds ratio of at least about 1.2, including by not limited to: 1.2, 1.3, 1.4, 1.5, 1.6, 1.7, 1.8, and 1.9. In a further embodiment, an odds ratio of at least 1.2 is significant. In a further embodiment, an odds ratio of at least about 1.5 is significant. In a further embodiment, a significant increase in risk is at least about 1.7 is significant. In a further embodiment, a significant increase in risk is at least about 20%, including but not limited to about 25%, 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, 75%, 80%, 85%, 90%, 95%, and 98%. In a further embodiment, a significant increase in risk is at least about 50%. In yet another embodiment, an at-risk haplotype has a p value < 0.05. It is understood however, that identifying whether a risk is medically significant may also depend on a variety of factors, including the specific disease, the haplotype, and often, environmental factors.

Particular embodiments of the invention encompass methods including a method of diagnosing a susceptibility to MI or ACS in an individual, comprising assessing in an individual the presence or frequency of SNPs and/or microsatellites in, comprising portions of, the LTA4H gene, wherein an excess or higher frequency of the SNPs and/or microsatellites in the individual, compared to a healthy control individual, is indicative that the individual is susceptible to MI or ACS. See, for example, Table 3, 4 and/or 5 (below) for SNPs and markers that can form haplotypes that can be used as screening tools, as well as Tables 4 and/or 5 for haplotypes that can be used for screening tools. Other particular embodiments of the invention encompass methods of diagnosing a susceptibility to MI or ACS in an individual, comprising detecting one or more markers at one or more polymorphic sites, wherein the one or more polymomrphic sites are in linkage disequilibrium with LTA4H.

Individuals who have been identified as being susceptible to MI or ACS using the methods described herein are individuals who fall within a target population for the methods of therapy described herein.

METHODS OF THERAPY

The present invention encompasses methods of treatment (prophylactic and/or therapeutic) for MI or ACS in individuals, such as individuals in the target populations described above, as well as for other diseases and conditions associated with LTA4H or with other members of the leukotriene pathway (*e.g.*, for atherosclerosis). Members of the "leukotriene pathway," as used herein, include polypeptides (*e.g.*, enzymes, receptors) and other molecules that are associated with production of leukotrienes: for example, enzymes such as LTA4H; other leukotriene biosynthetic enzymes (*e.g.*, FLAP, 5-LO); receptors or binding agents of the enzymes; leukotrienes such as LTA4, and LTB4; and receptors of leukotrienes (*e.g.*, leukotriene B4 receptor 1 (BLT1), leukotriene B4 receptor 2 (BLT2)).

In particular, the invention relates to methods of treatment for myocardial infarction or susceptibility to myocardial infarction (for example, for individuals in an at-risk population such as those described above); as well as methods of treatment for acute coronary syndrome (*e.g.*, unstable angina, non-ST-elevation myocardial infarction (NSTEMI) or ST-elevation myocardial infarction (STEMI)); for decreasing risk of a second myocardial infarction; for atherosclerosis, such as for patients requiring treatment (*e.g.*, angioplasty, stenting, coronary artery bypass graft) to restore blood flow in arteries (*e.g.*, coronary arteries); and/or for decreasing leukotriene synthesis (*e.g.*, for preventing and/or treatment of MI or ACS).

The invention additionally pertains to use of one or more leukotriene synthesis inhibitors, as described herein, for the manufacture of a medicament for the treatment of MI, ACS, and/or atherosclerosis, *e.g.*, using the methods described herein.

In the methods of the invention, a "leukotriene synthesis inhibitor" is used. In one embodiment, a "leukotriene synthesis inhibitor" is an agent that inhibits LTA4H polypeptide activity and/or LTA4H nucleic acid expression, as described herein. In

another embodiment, a leukotriene synthesis inhibitor is an agent that inhibits polypeptide activity and/or nucleic acid expression of another member of the leukotriene biosynthetic pathway (*e.g.*, FLAP, 5-LO). In still another embodiment, a leukotriene synthesis inhibitor is an agent that alters activity or metabolism of a leukotriene (*e.g.*, an antagonist of a leukotriene; an antagonist of a leukotriene receptor). In preferred embodiments, the leukotriene synthesis inhibitor decreases activity and/or nucleic acid expression of LTA4H.

Leukotriene synthesis inhibitors can alter polypeptide activity or nucleic acid expression of a member of the leukotriene pathway by a variety of means, such as, for example, by catalytically degrading, downregulating or interfering with the expression, transcription or translation of a nucleic acid encoding the member of the leukotriene pathway; by altering posttranslational processing of the polypeptide; by altering transcription of splicing variants; or by interfering with polypeptide activity (*e.g.*, by binding to the polypeptide, or by binding to another polypeptide that interacts with that member of the leukotriene pathway, such as an LTA4H binding agent as described herein or some other binding agent of a member of the leukotriene pathway; by altering interaction among two or more members of the leukotriene pathway (*e.g.*, interaction between FLAP and 5-LO); or by antagonizing activity of a member of the leukotriene pathway.

Representative leukotriene synthesis inhibitors include the following:

agents that inhibit activity of a member of the leukotriene biosynthetic pathway (*e.g.*, LTA4, FLAP, 5-LO), such as the agents presented in the Agent Table or in the Additional LTA4H Agent List below;

agents that inhibit activity of receptors of members of the leukotriene pathway, such as 5-LO receptors (*e.g.*, FLAP), LTB4 receptors (*e.g.*, BLT1, BLT2); agents that bind to the members of the leukotriene pathway, such as LTA4H binding agents, agents that bind to receptors of members of the leukotriene

pathway (*e.g.*, leukotriene receptor antagonists); or agents that bind to a leukotriene (*e.g.*, to LTA4, LTB4) or otherwise affect (*e.g.*, decrease) activity of the leukotriene;

antibodies to leukotrienes;

antisense nucleic acids or small double-stranded interfering RNA, to nucleic acids encoding LTA4H, or a leukotriene synthetase or other member of the leukotriene pathway (*e.g.*, FLAP, 5-LO), or fragments or derivatives thereof, including antisense nucleic acids to nucleic acids encoding the LTA4H, or leukotriene synthetase polypeptides, and vectors comprising such antisense nucleic acids (*e.g.*, nucleic acid, cDNA, and/or mRNA, double-stranded interfering RNA, or a nucleic acid encoding an active fragment or derivative thereof, or an oligonucleotide; for example, the complement of one of SEQ ID Nos. 1 or 2, or a nucleic acid complementary to the nucleic acid encoding SEQ ID NO: 3, or fragments or derivatives thereof);

peptidomimetics; fusion proteins or prodrugs thereof; ribozymes; other small molecules; and

other agents that alter (*e.g.*, inhibit or antagonize) expression of a member of the leukotriene pathway, such as LTA4H nucleic acid expression or polypeptide activity, or that regulate transcription of LTA4H splicing variants (*e.g.*, agents that affect which splicing variants are expressed, or that affect the amount of each splicing variant that is expressed).

More than one leukotriene synthesis inhibitor can be used concurrently, if desired.

The therapy is designed to alter activity of an LTA4H polypeptide, or another member of the leukotriene pathway in an individual, such as by inhibiting or

antagonizing activity. For example, a leukotriene synthesis inhibitor can be administered in order to decrease synthesis of leukotrienes within the individual, or to downregulate or decrease the expression or availability of the LTA4H nucleic acid or specific splicing variants of the LTA4H nucleic acid. Downregulation or decreasing expression or availability of a native LTA4H nucleic acid or of a particular splicing variant could minimize the expression or activity of a defective nucleic acid or the particular splicing variant and thereby minimize the impact of the defective nucleic acid or the particular splicing variant.

The leukotriene synthesis inhibitor(s) are administered in a therapeutically effective amount (*i.e.*, an amount that is sufficient to treat the disease or condition, such as by ameliorating symptoms associated with the disease or condition, preventing or delaying the onset of the disease or condition, and/or also lessening the severity or frequency of symptoms of the disease or condition). The amount which will be therapeutically effective in the treatment of a particular individual's disease or condition will depend on the symptoms and severity of the disease, and can be determined by standard clinical techniques. In addition, *in vitro* or *in vivo* assays may optionally be employed to help identify optimal dosage ranges. The precise dose to be employed in the formulation will also depend on the route of administration, and the seriousness of the disease or disorder, and should be decided according to the judgment of a practitioner and each patient's circumstances. Effective doses may be extrapolated from dose-response curves derived from *in vitro* or animal model test systems.

In preferred embodiments of the invention, the leukotriene synthesis inhibitor agent is an agent that inhibits activity of LTA4H. Preferred agents include the following, as set forth in the Agent Table or in the Additional LTA4H Agent List:

AGENT TABLE

Target	Compound ID	Chemical Name	Patent / Reference
LTA4H Inhibitor	SC-57461A	3-[methyl[3-[4-(phenylmethyl)phenoxy]-propyl]amino]propionic acid	Penning, T.D. et.al. Bioorg Med. Chem. Letters (2003), 13, 1137-1139. ibid, (2002), 12, 3383-3386
LTA4H Inhibitor	SC-56938	Ethyl-1-[2-[4-(phenylmethyl)phenoxy]ethyl]-4-piperidine-carboxylate	Penning, T.D. et.al. Bioorg Med. Chem. Letters (2003), 13, 1137-1139; ibid, (2002), 12, 3383-3386. US6506876A1
LTA4H Inhibitor	RP 64966	[4-[5-(3-Phenyl-propyl)thiophen-2-yl]butoxy]acetic acid	WO9627585
LTA4H Inhibitor	SA 6541	(R)-S-[[4-(dimethylamino)phenyl]methyl]-N-(3-mercapto-2methyl-1-oxopropyl-L-cycteine	WO9809943
LTB4 Receptor Antagonist	Amelubant / BIIL-284	Carbamic acid,((4-((3-((4-(1-(4-hydroxyphenyl)-1-methylethyl)phenoxy)methyl)phenyl)me thoxy)phenyl)iminomethyl)-ethyl ester	US 6,576,669
LTB4 Receptor Antagonist	BIRZ-227	5-Chloro-2-[3-(4-methoxy-phenyl)-2-pyridin-2-yl-pyrrolidin-1-yl]-benzooxazole	Journal of Organic Chemistry 1998,63:2(326-330).
LTB4 Receptor Antagonist	CP 195543	2-[(3S,4R)-3,4-dihydro-4-hydroxy-3-(phenylmethyl)-2H-1-benzopyran-7 -yl]-4-(trifluoromethyl)benzoic acid	Process: WO 98/11085 1998, priority US 60/26372 1996; J. Pharamacology and Expert. Therapy, 1998, 285: 946-54
LTB4 Receptor Antagonist	Ebselen	2-Phenyl-benzo[d]isoselenazol-3-one	Journal of Cerebral Blood Flow and Metabolism 1995, July 2-6 (S162); Drugs of the Future 1995, 20:10 (1057)
LTB4 Receptor Antagonist	LTB 019; CGS-25019C	4-[5-(4-Carbamimidoyl-phenoxy)-pentyloxy]-N,N-diisopropyl-3-methoxy-benzamide maleate	ACS Meeting 1994, 207th:San Diego (MEDI 003); International Congress of the Inflammation Research Association 1994, 7th:White Haven (Abs W23)
LTB4 Receptor Antagonist	LY 210073	5-(2-Carboxy-ethyl)-6-[6-(4-methoxy-phenyl)-hex-5-enyloxy]-9-oxo-9H-xanthene-2-carboxylic acid	J Med Chem 1993 36 (12) 1726-1734
LTB4 Receptor Antagonist	LY 213024	5-(3-carboxybenzoyl)-2-(decyloxy)benzenepropanoic acid	J Med Chem 1993 36 (12) 1726-1734

LTB4 Receptor Antagonist	LY 255283	1-[5-ethyl-2-hydroxy-4-[[6-methyl-6-(1H-tetrazol-5-yl)heptyl]oxy]ph enyl]ethanone	EP 276064 B 1990, priority US 2479 1987
LTB4 Receptor Antagonist	LY 264086	7-carboxy-3-(decyloxy)-9-oxo-9H-xanthene-4-propanoic acid	US 4996230 1991, priority US 481413 1990
LTB4 Receptor Antagonist	LY 292728	7-carboxy-3-[3-[(5-ethyl-4'-fluoro-2-hydroxy[1,1'-biphenyl]-4-yl)ox y]propoxy]-9-oxo-9H-xanthene-4-propanoic acid disodium salt	EP 743064 A 1996, priority US 443179 1995
LTB4 Receptor Antagonist	LY-293111 (VML-295)	Benzoic acid,2-(3-(3-((5-ethyl-4'-fluoro-2-hydroxy(1,1'-biphenyl)-4-yl)oxy)propoxy)-2-propylphenoxy)-	Proceedings of the American Society for Clinical Oncology 2002, 21:1 (Abs 343) [LY-293111 for Cancer] SCRIP World Pharmaceutical News 1997, 2272 (13) [for VML-295]
LTB4 Receptor Antagonist	ONO 4057; LB 457	(E)-2-(4-carboxybutoxy)-6-[[6-(4-methoxyphenyl)-5-hexenyl]oxy]benzenepropan oic acid	EP 405116 A 1991
LTB4 Receptor Antagonist	PF 10042	1-[5-hydroxy-5-[8-(1-hydroxy-2-phenylethyl)-2-dibenzofuranyl]-1-oxo pentyl]pyrrolidine	EP 422329 B 1995, priority US 409630 1989
LTB4 Receptor Antagonist	RG-14893	8-Benzyloxy-4-[(methyl-phenethyl-carbamoyl)-methyl]-naphthalene-2-carboxylic acid	SCRIP World Pharmaceutical News 1996, 2168 (20)
LTB4 Receptor Antagonist	SB-201993	3-{6-(2-Carboxy-vinyl)-5-[8-(4-methoxy-phenyl)-octyloxy]-pyridin-2-ylmethylsulfanylmethyl}-benzoic acid	WO-09500487
LTB4 Receptor Antagonist	SC-52798	7-[3-(2-Cyclopropylmethyl-3-methoxy-4-thiazol-4-yl-phenoxy)-propoxy]-8-propyl-chroman-2-carboxylic acid	Bioorganic and Medicinal Chemistry Letters 1994, 4:6 (811-816); Journal of Medicinal Chemistry 1995, 38:6 (858-868)
LTB4 Receptor Antagonist	SC-53228	3-{7-[3-(2-Cyclopropylmethyl-3-methoxy-4-methylcarbamoyl-phenoxy)-propoxy]-8-propyl-chroman-2-yl}-propionic acid	International Congress of the Inflammation Research Association 1994, 7th:White Haven (Abs W5)
LTB4 Receptor Antagonist	WAY 121006	3-fluoro-4'-(2-quinolinylmethoxy)-[1,1'-biphenyl]-4-acetic acid	Drugs under Experimental and Clinical research 1991, 17:8 (381-387)
LTB4 Receptor Antagonist	ZD-2138	3-Amino-3-(4-methoxy-tetrahydro-pyran-4-yl)-acrylic acid 1-methyl-2-oxo-1,2-dihydro-quinolin-6-ylmethyl ester	International Symposium on Medicinal Chemistry 1994, 13th:Paris (P 197)

In addition the following LTA4H inhibitors are described in USP2003/0004101A1, the teachings of which are incorporated herein by reference in their entirety:

ADDITIONAL LTA4H AGENT LIST

1. 1-[2-[4-(phenylmethyl)phenoxy]ethyl]-2-methyl-4-tetrazolylpieridine
2. 1-[2-[4-(4-oxazolyl)phenoxy)phenoxy]ethyl]pyrrolidine
3. 3-[methyl[3-[4-(2-thienylmethyl)phenoxy]propyl]amino]propionic acid
4. methyl 3-[methyl[3-[4-(2-thienylmethyl)phenoxy]propyl]amino]propionate
5. 3-[methyl[3-[4-(3-thienylmethyl)phenoxy]propyl]amino]propionic acid
6. methyl-3-[methyl[3-4-(3-theinylmethyl)phenoxy]propyl]amino]propionate
7. 3-[methyl[3-[4-(4-fluorophenoxy)phenoxy]propyl]amino]propionic acid
8. 3-[methyl[3-[4-(4-biphenyloxy)phenoxy]propyl]amino]propionic acid
9. N-[3-[[3-[4-(phenylmethyl)phenoxy] propyl]methylamino]propionyl]benzenesulfonamide
10. 1-[2-[4-(phenylmethyl)phenoxy]ethyl]-2-methyl-4-(1H-tetrazol-5-yl)piperidine
11. 1-[2-[4-(phenylmethyl)phenoxy]ethyl]-4-(1H-tetrazol-5-yl)piperidine

NUCLEIC ACID THERAPEUTIC AGENTS

In another embodiment, a nucleic acid of the invention; a nucleic acid complementary to a nucleic acid of the invention; or a portion of such a nucleic acid (*e.g.*, an oligonucleotide as described below); or a nucleic acid encoding a member of the leukotriene pathway (*e.g.*, LTA4H), can be used in "antisense" therapy, in which a nucleic acid (*e.g.*, an oligonucleotide) which specifically hybridizes to the mRNA and/or genomic DNA of a nucleic acid is administered or generated *in situ*. The antisense nucleic acid that specifically hybridizes to the mRNA and/or DNA inhibits

expression of the polypeptide encoded by that mRNA and/or DNA, *e.g.*, by inhibiting translation and/or transcription. Binding of the antisense nucleic acid can be by conventional base pair complementarity, or, for example, in the case of binding to DNA duplexes, through specific interaction in the major groove of the double helix.

An antisense construct can be delivered, for example, as an expression plasmid as described above. When the plasmid is transcribed in the cell, it produces RNA that is complementary to a portion of the mRNA and/or DNA that encodes the polypeptide for the member of the leukotriene pathway (*e.g.*, LTA4H). Alternatively, the antisense construct can be an oligonucleotide probe that is generated *ex vivo* and introduced into cells; it then inhibits expression by hybridizing with the mRNA and/or genomic DNA of the polypeptide. In one embodiment, the oligonucleotide probes are modified oligonucleotides that are resistant to endogenous nucleases, *e.g.*, exonucleases and/or endonucleases, thereby rendering them stable *in vivo*. Exemplary nucleic acid molecules for use as antisense oligonucleotides are phosphoramidate, phosphothioate and methylphosphonate analogs of DNA (see also U.S. Pat. Nos. 5,176,996, 5,264,564 and 5,256,775). Additionally, general approaches to constructing oligomers useful in antisense therapy are also described, for example, by Van der Krol *et al.* (*Biotechniques* 6:958-976 (1988)); and Stein *et al.* (*Cancer Res.* 48:2659-2668 (1988)). With respect to antisense DNA, oligodeoxyribonucleotides derived from the translation initiation site are preferred.

To perform antisense therapy, oligonucleotides (mRNA, cDNA or DNA) are designed that are complementary to mRNA encoding the polypeptide. The antisense oligonucleotides bind to mRNA transcripts and prevent translation. Absolute complementarity, although preferred, is not required. A sequence "complementary" to a portion of an RNA, as referred to herein, indicates that a sequence has sufficient complementarity to be able to hybridize with the RNA, forming a stable duplex; in the case of double-stranded antisense nucleic acids, a single strand of the duplex DNA may thus be tested, or triplex formation may be assayed. The ability to hybridize will depend on both the degree of complementarity and the length of the antisense nucleic acid, as described in detail above. Generally, the longer the hybridizing nucleic acid,

the more base mismatches with an RNA it may contain and still form a stable duplex (or triplex, as the case may be). One skilled in the art can ascertain a tolerable degree of mismatch by use of standard procedures.

The oligonucleotides used in antisense therapy can be DNA, RNA, or chimeric mixtures or derivatives or modified versions thereof, single-stranded or double-stranded. The oligonucleotides can be modified at the base moiety, sugar moiety, or phosphate backbone, for example, to improve stability of the molecule, hybridization, etc. The oligonucleotides can include other appended groups such as peptides (*e.g.* for targeting host cell receptors *in vivo*), or agents facilitating transport across the cell membrane (see, *e.g.*, Letsinger *et al.*, *Proc. Natl. Acad. Sci. USA* 86:6553-6556 (1989); Lemaitre *et al.*, *Proc. Natl. Acad. Sci. USA* 84:648-652 (1987); PCT International Publication No. WO 88/09810) or the blood-brain barrier (see, *e.g.*, PCT International Publication No. WO 89/10134), or hybridization-triggered cleavage agents (see, *e.g.*, Krol *et al.*, *BioTechniques* 6:958-976 (1988)) or intercalating agents. (See, *e.g.*, Zon, Pharm.Res. 5: 539-549 (1988)). To this end, the oligonucleotide may be conjugated to another molecule (*e.g.*, a peptide, hybridization triggered cross-linking agent, transport agent, hybridization-triggered cleavage agent).

The antisense molecules are delivered to cells that express the member of the leukotriene pathway *in vivo*. A number of methods can be used for delivering antisense DNA or RNA to cells; *e.g.*, antisense molecules can be injected directly into the tissue site, or modified antisense molecules, designed to target the desired cells (*e.g.*, antisense linked to peptides or antibodies that specifically bind receptors or antigens expressed on the target cell surface) can be administered systematically. Alternatively, in a preferred embodiment, a recombinant DNA construct is utilized in which the antisense oligonucleotide is placed under the control of a strong promoter (*e.g.*, pol III or pol II). The use of such a construct to transfect target cells in the patient results in the transcription of sufficient amounts of single stranded RNAs that will form complementary base pairs with the endogenous transcripts and thereby prevent translation of the mRNA. For example, a vector can be introduced *in vivo* such that it is taken up by a cell and directs the transcription of an antisense RNA.

Such a vector can remain episomal or become chromosomally integrated, as long as it can be transcribed to produce the desired antisense RNA. Such vectors can be constructed by recombinant DNA technology methods standard in the art and described above. For example, a plasmid, cosmid, YAC or viral vector can be used to prepare the recombinant DNA construct that can be introduced directly into the tissue site. Alternatively, viral vectors can be used which selectively infect the desired tissue, in which case administration may be accomplished by another route (*e.g.*, systemically).

In another embodiment of the invention, small double-stranded interfering RNA (RNA interference (RNAi)) can be used. RNAi is a post-transcription process, in which double-stranded RNA is introduced, and sequence-specific gene silencing results, though catalytic degradation of the targeted mRNA. See, *e.g.*, Elbashir, S.M. *et al.*, *Nature 411*:494-498 (2001); Lee, N.S., *Nature Biotech. 19*:500-505 (2002); Lee, S-K. *et al.*, *Nature Medicine 8(7)*:681-686 (2002); the entire teachings of these references are incorporated herein by reference.

Endogenous expression of a member of the leukotriene pathway (*e.g.*, LTA4H) can also be reduced by inactivating or "knocking out" the gene or its promoter using targeted homologous recombination (*e.g.*, see Smithies *et al.*, *Nature* 317:230-234 (1985); Thomas & Capecchi, *Cell* 51:503-512 (1987); Thompson *et al.*, *Cell* 5:313-321 (1989)). For example, an altered, non-functional gene of a member of the leukotriene pathway (or a completely unrelated DNA sequence) flanked by DNA homologous to the endogenous gene (either the coding regions or regulatory regions of the gene) can be used, with or without a selectable marker and/or a negative selectable marker, to transfect cells that express the gene *in vivo*. Insertion of the DNA construct, via targeted homologous recombination, results in inactivation of the gene. The recombinant DNA constructs can be directly administered or targeted to the required site *in vivo* using appropriate vectors, as described above. Alternatively, expression of non-altered genes can be increased using a similar method: targeted homologous recombination can be used to insert a DNA construct comprising a non-altered functional gene, or the complement thereof, or a portion thereof, in place of an

gene in the cell, as described above. In another embodiment, targeted homologous recombination can be used to insert a DNA construct comprising a nucleic acid that encodes a polypeptide variant that differs from that present in the cell.

Alternatively, endogenous expression of a member of the leukotriene pathway can be reduced by targeting deoxyribonucleotide sequences complementary to the regulatory region of the member of the leukotriene pathway (*i.e.*, the promoter and/or enhancers) to form triple helical structures that prevent transcription of the gene in target cells in the body. (See generally, Helene, C., *Anticancer Drug Des.*, 6(6):569-84 (1991); Helene, C. *et al.*, *Ann. N.Y. Acad. Sci.* 660:27-36 (1992); and Maher, L. J., *Bioassays* 14(12):807-15 (1992)). Likewise, the antisense constructs described herein, by antagonizing the normal biological activity of one of the members of the leukotriene pathway, can be used in the manipulation of tissue, *e.g.*, tissue differentiation, both *in vivo* and *for ex vivo* tissue cultures. Furthermore, the anti-sense techniques (*e.g.*, microinjection of antisense molecules, or transfection with plasmids whose transcripts are anti-sense with regard to a nucleic acid RNA or nucleic acid sequence) can be used to investigate the role of one or more members of the leukotriene pathway in the development of disease-related conditions. Such techniques can be utilized in cell culture, but can also be used in the creation of transgenic animals.

The therapeutic agents as described herein can be delivered in a composition, as described above, or by themselves. They can be administered systemically, or can be targeted to a particular tissue. The therapeutic agents can be produced by a variety of means, including chemical synthesis; recombinant production; *in vivo* production (*e.g.*, a transgenic animal, such as U.S. Pat. No. 4,873,316 to Meade *et al.*), for example, and can be isolated using standard means such as those described herein. In addition, a combination of any of the above methods of treatment (*e.g.*, administration of non-altered polypeptide in conjunction with antisense therapy targeting altered mRNA for a member of the leukotriene pathway; administration of a first splicing variant in conjunction with antisense therapy targeting a second splicing variant) can also be used.

The invention additionally pertains to use of such therapeutic agents, as described herein, for the manufacture of a medicament for the treatment of MI, ACS, and/or atherosclerosis, *e.g.*, using the methods described herein.

MONITORING PROGRESS OF TREATMENT

The current invention also pertains to methods of monitoring the response of an individual, such as an individual in one of the target populations described above, to treatment with a leukotriene synthesis inhibitor. Because the level of inflammatory markers can be elevated in individuals who are in the target populations described above, an assessment of the level of inflammatory markers of the individual both before, and during, treatment with the leukotriene synthesis inhibitor will indicate whether the treatment has successfully decreased production of leukotrienes in the arterial vessel wall or in bone-marrow derived inflammatory cells.

For example, in one embodiment of the invention, an individual who is a member of a target population of individuals at risk for MI or ACS (*e.g.*, an individual in a target population described above, such as an individual at-risk due to an LTA4H MI-haplotype) can be assessed for response to treatment with a leukotriene synthesis inhibitor, by examining leukotriene levels in the individual. Serum, plasma or urinary leukotrienes (*e.g.*, LTB4, LTE4, LTC4, LTD4), or *ex vivo* production of leukotrienes (*e.g.*, in blood samples stimulated with a calcium ionophore to produce leukotrienes) can be measured before, and during or after treatment with the leukotriene synthesis inhibitor. The leukotriene level before treatment is compared with the leukotriene level during or after treatment. The efficacy of treatment is indicated by a decrease in leukotriene production: a level of leukotriene during or after treatment that is significantly lower than the level of leukotriene before treatment, is indicative of efficacy. A level that is lower during or after treatment can be shown, for example, by decreased serum or urinary leukotrienes, or decreased *ex vivo* production of leukotrienes. A level that is "significantly lower", as used herein, is a level that is less than the amount that is typically found in control individual(s), or is less in a comparison of disease risk in a population associated with the other bands of

measurement (*e.g.*, the mean or median, the highest quartile or the highest quintile) compared to lower bands of measurement (*e.g.*, the mean or median, the other quartiles; the other quintiles).

In another embodiment of the invention, an individual who is a member of a target population of individuals at risk for MI or ACS (*e.g.*, an individual in a target population described above, such as an individual at-risk due to elevated C-reactive protein) can be assessed for response to treatment with a leukotriene synthesis inhibitor, by examining levels of inflammatory markers in the individual. For example, levels of an inflammatory marker in an appropriate test sample (*e.g.*, serum, plasma or urine) can be measured before, and during or after treatment with the leukotriene synthesis inhibitor. The level of the inflammatory marker before treatment is compared with the level of the inflammatory marker during or after treatment. The efficacy of treatment is indicated by a decrease in the level of the inflammatory marker, that is, a level of the inflammatory marker during or after treatment that is significantly lower than the level of inflammatory marker before treatment is indicative of efficacy. Representative inflammatory markers include: C-reactive protein (CRP), serum amyloid A, myeloperoxidase (MPO), N-tyrosine, di-tyrosine, lipoprotein phospholipase A2 (Lp-PLA2), fibrinogen, a leukotriene, a leukotriene metabolite (*e.g.*, cysteinyl leukotrienes), interleukin-6, tissue necrosis factor-alpha, soluble vascular cell adhesion molecules (sVCAM), soluble intervascular adhesion molecules (sICAM), E-selectin, matrix metalloprotease type-1, matrix metalloprotease type-2, matrix metalloprotease type-3, and matrix metalloprotease type-9. In a preferred embodiment, the marker is CRP.

PHARMACEUTICAL COMPOSITIONS

The present invention also pertains to pharmaceutical compositions comprising agents described herein, for example, an agent that is a leukotriene synthesis inhibitor as described herein. For instance, a leukotriene synthesis inhibitor can be formulated with a physiologically acceptable carrier or excipient to prepare a

pharmaceutical composition. The carrier and composition can be sterile. The formulation should suit the mode of administration.

Suitable pharmaceutically acceptable carriers include but are not limited to water, salt solutions (*e.g.*, NaCl), saline, buffered saline, alcohols, glycerol, ethanol, gum arabic, vegetable oils, benzyl alcohols, polyethylene glycols, gelatin, carbohydrates such as lactose, amylose or starch, dextrose, magnesium stearate, talc, silicic acid, viscous paraffin, perfume oil, fatty acid esters, hydroxymethylcellulose, polyvinyl pyrolidone, etc., as well as combinations thereof. The pharmaceutical preparations can, if desired, be mixed with auxiliary agents, *e.g.*, lubricants, preservatives, stabilizers, wetting agents, emulsifiers, salts for influencing osmotic pressure, buffers, coloring, flavoring and/or aromatic substances and the like which do not deleteriously react with the active agents.

The composition, if desired, can also contain minor amounts of wetting or emulsifying agents, or pH buffering agents. The composition can be a liquid solution, suspension, emulsion, tablet, pill, capsule, sustained release formulation, or powder. The composition can be formulated as a suppository, with traditional binders and carriers such as triglycerides. Oral formulation can include standard carriers such as pharmaceutical grades of mannitol, lactose, starch, magnesium stearate, polyvinyl pyrollidone, sodium saccharine, cellulose, magnesium carbonate, etc.

Methods of introduction of these compositions include, but are not limited to, intradermal, intramuscular, intraperitoneal, intraocular, intravenous, subcutaneous, topical, oral and intranasal. Other suitable methods of introduction can also include gene therapy (as described below), rechargeable or biodegradable devices, particle acceleration devices ("gene guns") and slow release polymeric devices. The pharmaceutical compositions of this invention can also be administered as part of a combinatorial therapy with other agents.

The composition can be formulated in accordance with the routine procedures as a pharmaceutical composition adapted for administration to human beings. For example, compositions for intravenous administration typically are solutions in sterile isotonic aqueous buffer. Where necessary, the composition may also include a

solubilizing agent and a local anesthetic to ease pain at the site of the injection. Generally, the ingredients are supplied either separately or mixed together in unit dosage form, for example, as a dry lyophilized powder or water free concentrate in a hermetically sealed container such as an ampule or sachette indicating the quantity of active agent. Where the composition is to be administered by infusion, it can be dispensed with an infusion bottle containing sterile pharmaceutical grade water, saline or dextrose/water. Where the composition is administered by injection, an ampule of sterile water for injection or saline can be provided so that the ingredients may be mixed prior to administration.

For topical application, nonsprayable forms, viscous to semi-solid or solid forms comprising a carrier compatible with topical application and having a dynamic viscosity preferably greater than water, can be employed. Suitable formulations include but are not limited to solutions, suspensions, emulsions, creams, ointments, powders, enemas, lotions, sols, liniments, salves, aerosols, etc., which are, if desired, sterilized or mixed with auxiliary agents, *e.g.*, preservatives, stabilizers, wetting agents, buffers or salts for influencing osmotic pressure, etc. The agent may be incorporated into a cosmetic formulation. For topical application, also suitable are sprayable aerosol preparations wherein the active ingredient, preferably in combination with a solid or liquid inert carrier material, is packaged in a squeeze bottle or in admixture with a pressurized volatile, normally gaseous propellant, *e.g.*, pressurized air.

Agents described herein can be formulated as neutral or salt forms. Pharmaceutically acceptable salts include those formed with free amino groups such as those derived from hydrochloric, phosphoric, acetic, oxalic, tartaric acids, etc., and those formed with free carboxyl groups such as those derived from sodium, potassium, ammonium, calcium, ferric hydroxides, isopropylamine, triethylamine, 2-ethylamino ethanol, histidine, procaine, etc.

The agents are administered in a therapeutically effective amount. The amount of agents which will be therapeutically effective in the treatment of a particular disorder or condition will depend on the nature of the disorder or condition,

and can be determined by standard clinical techniques. In addition, *in vitro* or *in vivo* assays may optionally be employed to help identify optimal dosage ranges. The precise dose to be employed in the formulation will also depend on the route of administration, and the seriousness of the symptoms, and should be decided according to the judgment of a practitioner and each patient's circumstances. Effective doses may be extrapolated from dose-response curves derived from *in vitro* or animal model test systems.

The invention also provides a pharmaceutical pack or kit comprising one or more containers filled with one or more of the ingredients of the pharmaceutical compositions of the invention. Optionally associated with such container(s) can be a notice in the form prescribed by a governmental agency regulating the manufacture, use or sale of pharmaceuticals or biological products, which notice reflects approval by the agency of manufacture, use of sale for human administration. The pack or kit can be labeled with information regarding mode of administration, sequence of drug administration (*e.g.*, separately, sequentially or concurrently), or the like. The pack or kit may also include means for reminding the patient to take the therapy. The pack or kit can be a single unit dosage of the combination therapy or it can be a plurality of unit dosages. In particular, the agents can be separated, mixed together in any combination, present in a single vial or tablet. Agents assembled in a blister pack or other dispensing means is preferred. For the purpose of this invention, unit dosage is intended to mean a dosage that is dependent on the individual pharmacodynamics of each agent and administered in FDA approved dosages in standard time courses.

NUCLEIC ACIDS OF THE INVENTION

LTA4H Nucleic Acids, Portions and Variants

In addition, the invention pertains to isolated nucleic acid molecules comprising a human LTA4H nucleic acid. The term, "LTA4H nucleic acid," as used herein, refers to an isolated nucleic acid molecule encoding LTA4H polypeptide. The LTA4H nucleic acid molecules of the present invention can be RNA, for example,

mRNA, or DNA, such as cDNA and genomic DNA. DNA molecules can be double-stranded or single-stranded; single stranded RNA or DNA can be either the coding, or sense strand or the non-coding, or antisense strand. The nucleic acid molecule can include all or a portion of the coding sequence of the gene or nucleic acid and can further comprise additional non-coding sequences such as introns and non-coding 3' and 5' sequences (including regulatory sequences, for example, as well as promoters, transcription enhancement elements, splice donor/acceptor sites, etc.).

For example, an LTA4H nucleic acid can consist of SEQ ID NOs: 1 or 2 or the complement thereof, or to a portion or fragment of such an isolated nucleic acid molecule (*e.g.*, cDNA or the nucleic acid) that encodes LTA4H polypeptide (*e.g.*, a polypeptide such as SEQ ID NO: 3). In a preferred embodiment, the isolated nucleic acid molecule comprises a nucleic acid molecule selected from the group consisting of SEQ ID NOs: 1 or 2, or their complement thereof.

Additionally, the nucleic acid molecules of the invention can be fused to a marker sequence, for example, a sequence that encodes a polypeptide to assist in isolation or purification of the polypeptide. Such sequences include, but are not limited to, those that encode a glutathione-S-transferase (GST) fusion protein and those that encode a hemagglutinin A (HA) polypeptide marker from influenza.

An "isolated" nucleic acid molecule, as used herein, is one that is separated from nucleic acids that normally flank the gene or nucleic acid sequence (as in genomic sequences) and/or has been completely or partially purified from other transcribed sequences (*e.g.*, as in an RNA library). For example, an isolated nucleic acid of the invention may be substantially isolated with respect to the complex cellular milieu in which it naturally occurs, or culture medium when produced by recombinant techniques, or chemical precursors or other chemicals when chemically synthesized. In some instances, the isolated material will form part of a composition (for example, a crude extract containing other substances), buffer system or reagent mix. In other circumstances, the material may be purified to essential homogeneity, for example as determined by PAGE or column chromatography such as HPLC. In certain embodiments, an isolated nucleic acid molecule comprises at least about 50,

80 or 90% (on a molar basis) of all macromolecular species present. With regard to genomic DNA, the term "isolated" also can refer to nucleic acid molecules that are separated from the chromosome with which the genomic DNA is naturally associated. For example, the isolated nucleic acid molecule can contain less than about 5 kb, including but not limited to 4 kb, 3 kb, 2 kb, 1 kb, 0.5 kb or 0.1 kb of nucleotides which flank the nucleic acid molecule in the genomic DNA of the cell from which the nucleic acid molecule is derived.

The nucleic acid molecule can be fused to other coding or regulatory sequences and still be considered isolated. Thus, recombinant DNA contained in a vector is included in the definition of "isolated" as used herein. Also, isolated nucleic acid molecules include recombinant DNA molecules in heterologous host cells, as well as partially or substantially purified DNA molecules in solution. "Isolated" nucleic acid molecules also encompass *in vivo* and *in vitro* RNA transcripts of the DNA molecules of the present invention. An isolated nucleic acid molecule or nucleic acid sequence can include a nucleic acid molecule or nucleic acid sequence that is synthesized chemically or by recombinant means. Therefore, recombinant DNA contained in a vector is included in the definition of "isolated" as used herein. Also, isolated nucleotide sequences include recombinant DNA molecules in heterologous organisms, as well as partially or substantially purified DNA molecules in solution. *In vivo* and *in vitro* RNA transcripts of the DNA molecules of the present invention are also encompassed by "isolated" nucleotide sequences. Such isolated nucleotide sequences are useful in the manufacture of the encoded polypeptide, as probes for isolating homologous sequences (*e.g.*, from other mammalian species), for gene mapping (*e.g.*, by *in situ* hybridization with chromosomes), or for detecting expression of the nucleic acid in tissue (*e.g.*, human tissue), such as by Northern blot analysis.

The present invention also pertains to nucleic acid molecules which are not necessarily found in nature but which encode an LTA4H polypeptide (*e.g.*, a polypeptide having an amino acid sequence comprising an amino acid sequence of SEQ ID NO: 3), or another splicing variant of an LTA4H polypeptide or

polymorphic variant thereof. Thus, for example, DNA molecules that comprise a sequence that is different from the naturally occurring nucleic acid sequence but which, due to the degeneracy of the genetic code, encode an LTA4H polypeptide of the present invention are also the subjects of this invention. The invention also encompasses nucleotide sequences encoding portions (fragments), or encoding variant polypeptides such as analogues or derivatives of an LTA4H polypeptide. Such variants can be naturally occurring, such as in the case of allelic variation or single nucleotide polymorphisms, or non-naturally-occurring, such as those induced by various mutagens and mutagenic processes. Intended variations include, but are not limited to, addition, deletion and substitution of one or more nucleotides that can result in conservative or non-conservative amino acid changes, including additions and deletions. Preferably the nucleotide (and/or resultant amino acid) changes are silent or conserved; that is, they do not alter the characteristics or activity of an LTA4H polypeptide. In one preferred embodiment, the nucleotide sequences are fragments that comprise one or more polymorphic microsatellite markers. In another preferred embodiment, the nucleotide sequences are fragments that comprise one or more single nucleotide polymorphisms in an LTA4H nucleic acid (*e.g.*, the single nucleotide polymorphisms set forth in Table 3, below).

Other alterations of the nucleic acid molecules of the invention can include, for example, labeling, methylation, internucleotide modifications such as uncharged linkages (*e.g.*, methyl phosphonates, phosphotriesters, phosphoamidates, carbamates), charged linkages (*e.g.*, phosphorothioates, phosphorodithioates), pendent moieties (*e.g.*, polypeptides), intercalators (*e.g.*, acridine, psoralen), chelators, alkylators, and modified linkages (*e.g.*, alpha anomeric nucleic acids). Also included are synthetic molecules that mimic nucleic acid molecules in the ability to bind to a designated sequence via hydrogen bonding and other chemical interactions. Such molecules include, for example, those in which peptide linkages substitute for phosphate linkages in the backbone of the molecule.

The invention also pertains to nucleic acid molecules that hybridize under high stringency hybridization conditions, such as for selective hybridization, to a nucleic

acid sequence described herein (*e.g.*, nucleic acid molecules which specifically hybridize to a nucleic acid sequence encoding polypeptides described herein, and, optionally, have an activity of the polypeptide). In one embodiment, the invention includes variants described herein which hybridize under high stringency hybridization conditions (*e.g.*, for selective hybridization) to a nucleic acid sequence comprising a nucleic acid sequence selected from the group consisting of SEQ ID NOs: 1 or 2 or the complement thereof. In another embodiment, the invention includes variants described herein which hybridize under high stringency hybridization conditions (*e.g.*, for selective hybridization) to a nucleic acid sequence encoding an amino acid sequence of SEQ ID NO: 3 or a polymorphic variant thereof. In a preferred embodiment, the variant that hybridizes under high stringency hybridizations has an activity of LTA4H.

Such nucleic acid molecules can be detected and/or isolated by specific hybridization (*e.g.*, under high stringency conditions). "Specific hybridization," as used herein, refers to the ability of a first nucleic acid to hybridize to a second nucleic acid in a manner such that the first nucleic acid does not hybridize to any nucleic acid other than to the second nucleic acid (*e.g.*, when the first nucleic acid has a higher similarity to the second nucleic acid than to any other nucleic acid in a sample wherein the hybridization is to be performed). "Stringency conditions" for hybridization is a term of art which refers to the incubation and wash conditions, *e.g.*, conditions of temperature and buffer concentration, which permit hybridization of a particular nucleic acid to a second nucleic acid; the first nucleic acid may be perfectly (*i.e.*, 100%) complementary to the second, or the first and second may share some degree of complementarity that is less than perfect (*e.g.*, 70%, 75%, 85%, 95%). For example, certain high stringency conditions can be used which distinguish perfectly complementary nucleic acids from those of less complementarity. "High stringency conditions", "moderate stringency conditions" and "low stringency conditions" for nucleic acid hybridizations are explained on pages 2.10.1-2.10.16 and pages 6.3.1-6.3.6 in *Current Protocols in Molecular Biology* (Ausubel, F.M. *et al.*, "*Current Protocols in Molecular Biology*", John Wiley & Sons, (1998), the entire teachings of

which are incorporated by reference herein). The exact conditions which determine the stringency of hybridization depend not only on ionic strength (*e.g.*, 0.2X SSC, 0.1X SSC), temperature (*e.g.*, room temperature, 42°C, 68°C) and the concentration of destabilizing agents such as formamide or denaturing agents such as SDS, but also on factors such as the length of the nucleic acid sequence, base composition, percent mismatch between hybridizing sequences and the frequency of occurrence of subsets of that sequence within other non-identical sequences. Thus, equivalent conditions can be determined by varying one or more of these parameters while maintaining a similar degree of identity or similarity between the two nucleic acid molecules. Typically, conditions are used such that sequences at least about 60%, at least about 70%, at least about 80%, at least about 90% or at least about 95% or more identical to each other remain hybridized to one another. By varying hybridization conditions from a level of stringency at which no hybridization occurs to a level at which hybridization is first observed, conditions which will allow a given sequence to hybridize (*e.g.*, selectively) with the most similar sequences in the sample can be determined.

Exemplary conditions are described in Krause, M.H. and S.A. Aaronson, *Methods in Enzymology* 200: 546-556 (1991), and in, Ausubel, *et al.*, "*Current Protocols in Molecular Biology*", John Wiley & Sons, (1998), which describes the determination of washing conditions for moderate or low stringency conditions. Washing is the step in which conditions are usually set so as to determine a minimum level of complementarity of the hybrids. Generally, starting from the lowest temperature at which only homologous hybridization occurs, each °C by which the final wash temperature is reduced (holding SSC concentration constant) allows an increase by 1% in the maximum extent of mismatching among the sequences that hybridize. Generally, doubling the concentration of SSC results in an increase in T_m of -17°C. Using these guidelines, the washing temperature can be determined empirically for high, moderate or low stringency, depending on the level of mismatch sought.

For example, a low stringency wash can comprise washing in a solution containing 0.2X SSC/0.1% SDS for 10 minutes at room temperature; a moderate stringency wash can comprise washing in a prewarmed solution (42°C) solution containing 0.2X SSC/0.1% SDS for 15 minutes at 42°C; and a high stringency wash can comprise washing in prewarmed (68°C) solution containing 0.1X SSC/0.1%SDS for 15 minutes at 68°C. Furthermore, washes can be performed repeatedly or sequentially to obtain a desired result as known in the art. Equivalent conditions can be determined by varying one or more of the parameters given as an example, as known in the art, while maintaining a similar degree of identity or similarity between the target nucleic acid molecule and the primer or probe used.

The percent homology or identity of two nucleotide or amino acid sequences can be determined by aligning the sequences for optimal comparison purposes (*e.g.*, gaps can be introduced in the sequence of a first sequence for optimal alignment). The nucleotides or amino acids at corresponding positions are then compared, and the percent identity between the two sequences is a function of the number of identical positions shared by the sequences (*i.e.*, % identity = # of identical positions/total # of positions x 100). When a position in one sequence is occupied by the same nucleotide or amino acid residue as the corresponding position in the other sequence, then the molecules are homologous at that position. As used herein, nucleic acid or amino acid "homology" is equivalent to nucleic acid or amino acid "identity". In certain embodiments, the length of a sequence aligned for comparison purposes is at least 30%, for example, at least 40%, in certain embodiments at least 60%, and in other embodiments at least 70%, 80%, 90% or 95% of the length of the reference sequence. The actual comparison of the two sequences can be accomplished by well-known methods, for example, using a mathematical algorithm. A preferred, non-limiting example of such a mathematical algorithm is described in Karlin *et al.*, *Proc. Natl. Acad. Sci. USA* 90:5873-5877 (1993). Such an algorithm is incorporated into the NBLAST and XBLAST programs (version 2.0) as described in Altschul *et al.*, *Nucleic Acids Res.* 25:389-3402 (1997). When utilizing BLAST and Gapped BLAST programs, the default parameters of the respective programs (*e.g.*, NBLAST) can be

used. In one embodiment, parameters for sequence comparison can be set at score=100, wordlength=12, or can be varied (*e.g.*, W=5 or W=20).

Another preferred, non-limiting example of a mathematical algorithm utilized for the comparison of sequences is the algorithm of Myers and Miller, *CABIOS* 4(1): 11-17 (1988). Such an algorithm is incorporated into the ALIGN program (version 2.0) which is part of the GCG sequence alignment software package (Accelrys, Cambridge, UK). When utilizing the ALIGN program for comparing amino acid sequences, a PAM120 weight residue table, a gap length penalty of 12, and a gap penalty of 4 can be used. Additional algorithms for sequence analysis are known in the art and include ADVANCE and ADAM as described in Torellis and Robotti, *Comput. Appl. Biosci.* 10:3-5 (1994); and FASTA described in Pearson and Lipman, *Proc. Natl. Acad. Sci. USA* 85:2444-8 (1988).

In another embodiment, the percent identity between two amino acid sequences can be accomplished using the GAP program in the GCG software package using either a BLOSUM63 matrix or a PAM250 matrix, and a gap weight of 12, 10, 8, 6, or 4 and a length weight of 2, 3, or 4. In yet another embodiment, the percent identity between two nucleic acid sequences can be accomplished using the GAP program in the GCG software package using a gap weight of 50 and a length weight of 3.

The present invention also provides isolated nucleic acid molecules that contain a fragment or portion that hybridizes under highly stringent conditions to a nucleic acid sequence comprising SEQ ID NO: 1 or 2 or the complement of SEQ ID NO: 1 or 2, and also provides isolated nucleic acid molecules that contain a fragment or portion that hybridizes under highly stringent conditions to a nucleic acid sequence encoding an amino acid sequence of the invention or polymorphic variant thereof. The nucleic acid fragments of the invention are at least about 15, for example, at least about 18, 20, 23 or 25 nucleotides, and can be 30, 40, 50, 100, 200 or more nucleotides in length. Longer fragments, for example, 30 or more nucleotides in length, encoding antigenic polypeptides described herein are particularly useful, such as for the generation of antibodies as described below.

Probes and Primers

In a related aspect, the nucleic acid fragments of the invention are used as probes or primers in assays such as those described herein. "Probes" or "primers" are oligonucleotides that hybridize in a base-specific manner to a complementary strand of nucleic acid molecules. Such probes and primers include polypeptide nucleic acids, as described in Nielsen *et al.(Science* 254:1497-1500 (1991)).

A probe or primer comprises a region of nucleic acid that hybridizes to at least about 15, for example about 20-25, and in certain embodiments about 40, 50 or 75, consecutive nucleotides of a nucleic acid of the invention, such as a nucleic acid comprising a contiguous nucleic acid sequence of SEQ ID NOs: 1 or 2 or the complement of SEQ ID Nos: 1 or 2, or a nucleic acid sequence encoding an amino acid sequence of SEQ ID NO: 3 or polymorphic variant thereof. In preferred embodiments, a probe or primer comprises 100 or fewer nucleotides, in certain embodiments, from 6 to 50 nucleotides, for example, from 12 to 30 nucleotides. In other embodiments, the probe or primer is at least 70% identical to the contiguous nucleic acid sequence or to the complement of the contiguous nucleotide sequence, for example, at least 80% identical, in certain embodiments at least 90% identical, and in other embodiments at least 95% identical, or even capable of selectively hybridizing to the contiguous nucleic acid sequence or to the complement of the contiguous nucleotide sequence. Often, the probe or primer further comprises a label, *e.g.*, radioisotope, fluorescent compound, enzyme, or enzyme co-factor.

The nucleic acid molecules of the invention such as those described above can be identified and isolated using standard molecular biology techniques and the sequence information provided herein. For example, nucleic acid molecules can be amplified and isolated using the polymerase chain reaction and synthetic oligonucleotide primers based on one or more of SEQ ID NOs: 1 or 2, or the complement thereof, or designed based on nucleotides based on sequences encoding one or more of the amino acid sequences provided herein. See generally *PCR Technology: Principles and Applications for DNA Amplification* (ed. H.A. Erlich,

Freeman Press, NY, NY, 1992); *PCR Protocols: A Guide to Methods and Applications* (Eds. Innis *et al.*, Academic Press, San Diego, CA, 1990); Mattila *et al.*, *Nucl. Acids Res.* 19:4967 (1991); Eckert *et al.*, *PCR Methods and Applications* 1:17 (1991); PCR (eds. McPherson *et al.*, IRL Press, Oxford); and U.S. Patent 4,683,202. The nucleic acid molecules can be amplified using cDNA, mRNA or genomic DNA as a template, cloned into an appropriate vector and characterized by DNA sequence analysis.

Other suitable amplification methods include the ligase chain reaction (LCR) (see Wu and Wallace, *Genomics* 4:560 (1989), Landegren *et al.*, *Science* 241:1077 (1988), transcription amplification (Kwoh *et al.*, *Proc. Natl. Acad. Sci. USA* 86:1173 (1989)), and self-sustained sequence replication (Guatelli *et al.*, *Proc. Nat. Acad. Sci. USA* 87:1874 (1990)) and nucleic acid based sequence amplification (NASBA). The latter two amplification methods involve isothermal reactions based on isothermal transcription, which produce both single stranded RNA (ssRNA) and double stranded DNA (dsDNA) as the amplification products in a ratio of about 30 or 100 to 1, respectively.

The amplified DNA can be labeled, for example, radiolabeled, and used as a probe for screening a cDNA library derived from human cells, mRNA in zap express, ZIPLOX or other suitable vector. Corresponding clones can be isolated, DNA can obtained following *in vivo* excision, and the cloned insert can be sequenced in either or both orientations by art recognized methods to identify the correct reading frame encoding a polypeptide of the appropriate molecular weight. For example, the direct analysis of the nucleic acid molecules of the present invention can be accomplished using well-known methods that are commercially available. See, for example, Sambrook *et al.*, *Molecular Cloning, A Laboratory Manual* (2nd Ed., CSHP, New York 1989); Zyskind *et al.*, *Recombinant DNA Laboratory Manual*, (Acad. Press, 1988)). Using these or similar methods, the polypeptide and the DNA encoding the polypeptide can be isolated, sequenced and further characterized.

Antisense nucleic acid molecules of the invention can be designed using the nucleotide sequences of SEQ ID NOs: 1 or 2 and/or the complement of one or more

of SEQ ID NOs: 1 or 2 and/or a portion of one or more of SEQ ID NOs: 1 or 2 or the complement of one or more of SEQ ID NOs: 1 or 2 and/or a sequence encoding the amino acid sequence of SEQ ID NO: 3 or encoding a portion of SEQ ID NO: 3 or its complement. They can be constructed using chemical synthesis and enzymatic ligation reactions using procedures known in the art. For example, an antisense nucleic acid molecule (*e.g.*, an antisense oligonucleotide) can be chemically synthesized using naturally occurring nucleotides or variously modified nucleotides designed to increase the biological stability of the molecules or to increase the physical stability of the duplex formed between the antisense and sense nucleic acids, *e.g.*, phosphorothioate derivatives and acridine substituted nucleotides can be used. Alternatively, the antisense nucleic acid molecule can be produced biologically using an expression vector into which a nucleic acid molecule has been subcloned in an antisense orientation (*i.e.*, RNA transcribed from the inserted nucleic acid molecule will be of an antisense orientation to a target nucleic acid of interest).

The nucleic acid sequences can also be used to compare with endogenous DNA sequences in patients to identify one or more of the disorders related to LTA4H, and as probes, such as to hybridize and discover related DNA sequences or to subtract out known sequences from a sample. The nucleic acid sequences can further be used to derive primers for genetic fingerprinting, to raise anti-polypeptide antibodies using DNA immunization techniques, and as an antigen to raise anti-DNA antibodies or elicit immune responses. Portions or fragments of the nucleotide sequences identified herein (and the corresponding complete gene sequences) can be used in numerous ways as polynucleotide reagents. For example, these sequences can be used to: (i) map their respective genes on a chromosome; and, thus, locate gene regions or nucleic acid regions associated with genetic disease; (ii) identify an individual from a minute biological sample (tissue typing); and (iii) aid in forensic identification of a biological sample. Additionally, the nucleotide sequences of the invention can be used to identify and express recombinant polypeptides for analysis, characterization or therapeutic use, or as markers for tissues in which the corresponding polypeptide is expressed, either constitutively, during tissue differentiation, or in diseased states.

The nucleic acid sequences can additionally be used as reagents in the screening and/or diagnostic assays described herein, and can also be included as components of kits (*e.g.*, reagent kits) for use in the screening and/or diagnostic assays described herein.

Vectors

Another aspect of the invention pertains to nucleic acid constructs containing a nucleic acid molecule of SEQ ID NOs: 1 or 2 or the complement thereof (or a portion thereof). Yet another aspect of the invention pertains to nucleic acid constructs containing a nucleic acid molecule encoding an amino acid of SEQ ID NO: 3 or polymorphic variant thereof. The constructs comprise a vector (*e.g.*, an expression vector) into which a sequence of the invention has been inserted in a sense or antisense orientation. As used herein, the term "vector" refers to a nucleic acid molecule capable of transporting another nucleic acid to which it has been linked. One type of vector is a "plasmid", which refers to a circular double stranded DNA loop into which additional DNA segments can be ligated. Another type of vector is a viral vector, wherein additional DNA segments can be ligated into the viral genome. Certain vectors are capable of autonomous replication in a host cell into which they are introduced (*e.g.*, bacterial vectors having a bacterial origin of replication and episomal mammalian vectors). Other vectors (*e.g.*, non-episomal mammalian vectors) are integrated into the genome of a host cell upon introduction into the host cell, and thereby are replicated along with the host genome. Moreover, certain vectors, such as expression vectors, are capable of directing the expression of genes or nucleic acids to which they are operably linked. In general, expression vectors of utility in recombinant DNA techniques are often in the form of plasmids. However, the invention is intended to include such other forms of expression vectors, such as viral vectors (*e.g.*, replication defective retroviruses, adenoviruses and adeno-associated viruses) that serve equivalent functions.

Preferred recombinant expression vectors of the invention comprise a nucleic acid molecule of the invention in a form suitable for expression of the nucleic acid

molecule in a host cell. This means that the recombinant expression vectors include one or more regulatory sequences, selected on the basis of the host cells to be used for expression, which is operably linked to the nucleic acid sequence to be expressed. Within a recombinant expression vector, "operably linked" or "operatively linked" is intended to mean that the nucleic acid sequence of interest is linked to the regulatory sequence(s) in a manner which allows for expression of the nucleic acid sequence (*e.g.*, in an *in vitro* transcription/translation system or in a host cell when the vector is introduced into the host cell). The term "regulatory sequence" is intended to include promoters, enhancers and other expression control elements (*e.g.*, polyadenylation signals). Such regulatory sequences are described, for example, in Goeddel, "Gene Expression Technology", *Methods in Enzymology* 185, Academic Press, San Diego, CA (1990). Regulatory sequences include those which direct constitutive expression of a nucleic acid sequence in many types of host cell and those which direct expression of the nucleic acid sequence only in certain host cells (*e.g.*, tissue-specific regulatory sequences). It will be appreciated by those skilled in the art that the design of the expression vector can depend on such factors as the choice of the host cell to be transformed and the level of expression of polypeptide desired. The expression vectors of the invention can be introduced into host cells to thereby produce polypeptides, including fusion polypeptides, encoded by nucleic acid molecules as described herein.

The recombinant expression vectors of the invention can be designed for expression of a polypeptide of the invention in prokaryotic or eukaryotic cells, *e.g.*, bacterial cells such as *E. coli*, insect cells (using baculovirus expression vectors), yeast cells or mammalian cells. Suitable host cells are discussed further in Goeddel, *supra*. Alternatively, the recombinant expression vector can be transcribed and translated *in vitro*, for example using T7 promoter regulatory sequences and T7 polymerase.

Another aspect of the invention pertains to host cells into which a recombinant expression vector of the invention has been introduced. The terms "host cell" and "recombinant host cell" are used interchangeably herein. It is understood that such

terms refer not only to the particular subject cell but also to the progeny or potential progeny of such a cell. Because certain modifications may occur in succeeding generations due to either mutation or environmental influences, such progeny may not, in fact, be identical to the parent cell, but are still included within the scope of the term as used herein.

A host cell can be any prokaryotic or eukaryotic cell. For example, a nucleic acid molecule of the invention can be expressed in bacterial cells (*e.g.*, *E. coli*), insect cells, yeast or mammalian cells (such as Chinese hamster ovary cells (CHO) or COS cells). Other suitable host cells are known to those skilled in the art.

Vector DNA can be introduced into prokaryotic or eukaryotic cells via conventional transformation or transfection techniques. As used herein, the terms "transformation" and "transfection" are intended to refer to a variety of art-recognized techniques for introducing a foreign nucleic acid molecule (*e.g.*, DNA) into a host cell, including calcium phosphate or calcium chloride co-precipitation, DEAE-dextran-mediated transfection, lipofection, or electroporation. Suitable methods for transforming or transfecting host cells can be found in Sambrook, *et al.* (*supra*), and other laboratory manuals.

For stable transfection of mammalian cells, it is known that, depending upon the expression vector and transfection technique used, only a small fraction of cells may integrate the foreign DNA into their genome. In order to identify and select these integrants, a gene or nucleic acid that encodes a selectable marker (*e.g.*, for resistance to antibiotics) is generally introduced into the host cells along with the gene or nucleic acid of interest. Preferred selectable markers include those that confer resistance to drugs, such as G418, hygromycin and methotrexate. Nucleic acid molecules encoding a selectable marker can be introduced into a host cell on the same vector as the nucleic acid molecule of the invention or can be introduced on a separate vector. Cells stably transfected with the introduced nucleic acid molecule can be identified by drug selection (*e.g.*, cells that have incorporated the selectable marker gene or nucleic acid will survive, while the other cells die).

A host cell of the invention, such as a prokaryotic host cell or eukaryotic host cell in culture can be used to produce (*i.e.*, express) a polypeptide of the invention. Accordingly, the invention further provides methods for producing a polypeptide using the host cells of the invention. In one embodiment, the method comprises culturing the host cell of invention (into which a recombinant expression vector encoding a polypeptide of the invention has been introduced) in a suitable medium such that the polypeptide is produced. In another embodiment, the method further comprises isolating the polypeptide from the medium or the host cell.

The host cells of the invention can also be used to produce nonhuman transgenic animals. For example, in one embodiment, a host cell of the invention is a fertilized oocyte or an embryonic stem cell into which a nucleic acid molecule of the invention has been introduced (*e.g.*, an exogenous LTA4H nucleic acid, or an exogenous nucleic acid encoding an LTA4H polypeptide). Such host cells can then be used to create non-human transgenic animals in which exogenous nucleotide sequences have been introduced into the genome or homologous recombinant animals in which endogenous nucleotide sequences have been altered. Such animals are useful for studying the function and/or activity of the nucleic acid sequence and polypeptide encoded by the sequence and for identifying and/or evaluating modulators of their activity. As used herein, a "transgenic animal" is a non-human animal, preferably a mammal, more preferably a rodent such as a rat or mouse, in which one or more of the cells of the animal include a transgene. Other examples of transgenic animals include non-human primates, sheep, dogs, cows, goats, chickens and amphibians. A transgene is exogenous DNA which is integrated into the genome of a cell from which a transgenic animal develops and which remains in the genome of the mature animal, thereby directing the expression of an encoded gene product in one or more cell types or tissues of the transgenic animal. As used herein, an "homologous recombinant animal" is a non-human animal, preferably a mammal, more preferably a mouse, in which an endogenous gene has been altered by homologous recombination between the endogenous gene and an exogenous DNA

molecule introduced into a cell of the animal, *e.g.*, an embryonic cell of the animal, prior to development of the animal.

Methods for generating transgenic animals via embryo manipulation and microinjection, particularly animals such as mice, have become conventional in the art and are described, for example, in U.S. Patent Nos. 4,736,866 and 4,870,009, U.S. Pat. No. 4,873,191 and in Hogan, *Manipulating the Mouse Embryo* (Cold Spring Harbor Laboratory Press, Cold Spring Harbor, N.Y., 1986). Methods for constructing homologous recombination vectors and homologous recombinant animals are described further in Bradley, *Current Opinion in BioTechnology* 2:823-829 (1991) and in PCT Publication Nos. WO 90/11354, WO 91/01140, WO 92/0968, and WO 93/04169. Clones of the non-human transgenic animals described herein can also be produced according to the methods described in Wilmut *et al.*, *Nature* 385:810-813 (1997) and PCT Publication Nos. WO 97/07668 and WO 97/07669.

POLYPEPTIDES OF THE INVENTION

The present invention also pertains to isolated polypeptides encoded by LTA4H nucleic acids ("LTA4H polypeptides"), and fragments and variants thereof, as well as polypeptides encoded by nucleotide sequences described herein (*e.g.*, other splicing variants). The term "polypeptide" refers to a polymer of amino acids, and not to a specific length; thus, peptides, oligopeptides and proteins are included within the definition of a polypeptide. As used herein, a polypeptide is said to be "isolated" or "purified" when it is substantially free of cellular material when it is isolated from recombinant and non-recombinant cells, or free of chemical precursors or other chemicals when it is chemically synthesized. A polypeptide, however, can be joined to another polypeptide with which it is not normally associated in a cell (*e.g.*, in a "fusion protein") and still be "isolated" or "purified."

The polypeptides of the invention can be purified to homogeneity. It is understood, however, that preparations in which the polypeptide is not purified to homogeneity are useful. The critical feature is that the preparation allows for the desired function of the polypeptide, even in the presence of considerable amounts of

other components. Thus, the invention encompasses various degrees of purity. In one embodiment, the language "substantially free of cellular material" includes preparations of the polypeptide having less than about 30% (by dry weight) other proteins (*i.e.*, contaminating protein), less than about 20% other proteins, less than about 10% other proteins, or less than about 5% other proteins.

When a polypeptide is recombinantly produced, it can also be substantially free of culture medium, *i.e.*, culture medium represents less than about 20%, less than about 10%, or less than about 5% of the volume of the polypeptide preparation. The language "substantially free of chemical precursors or other chemicals" includes preparations of the polypeptide in which it is separated from chemical precursors or other chemicals that are involved in its synthesis. In one embodiment, the language "substantially free of chemical precursors or other chemicals" includes preparations of the polypeptide having less than about 30% (by dry weight) chemical precursors or other chemicals, less than about 20% chemical precursors or other chemicals, less than about 10% chemical precursors or other chemicals, or less than about 5% chemical precursors or other chemicals.

In one embodiment, a polypeptide of the invention comprises an amino acid sequence encoded by a nucleic acid molecule comprising a nucleic acid sequence selected from the group consisting of SEQ ID NO: 1 or 2, or the complement of SEQ ID NO: 1 or 2, or portions thereof, or a portion or polymorphic variant thereof. However, the polypeptides of the invention also encompass fragment and sequence variants. Variants include a substantially homologous polypeptide encoded by the same genetic locus in an organism, *i.e.*, an allelic variant, as well as other splicing variants. Variants also encompass polypeptides derived from other genetic loci in an organism, but having substantial homology to a polypeptide encoded by a nucleic acid molecule comprising a nucleic acid sequence selected from the group consisting of SEQ ID NOs: 1 or 2 or their complement, or portions thereof, or having substantial homology to a polypeptide encoded by a nucleic acid molecule comprising a nucleic acid sequence selected from the group consisting of nucleotide sequences encoding SEQ ID NO: 3 and polymorphic variants thereof. Variants also include polypeptides

substantially homologous or identical to these polypeptides but derived from another organism, *i.e.*, an ortholog. Variants also include polypeptides that are substantially homologous or identical to these polypeptides that are produced by chemical synthesis. Variants also include polypeptides that are substantially homologous or identical to these polypeptides that are produced by recombinant methods.

As used herein, two polypeptides (or a region of the polypeptides) are substantially homologous or identical when the amino acid sequences are at least about 45-55%, in certain embodiments at least about 70-75%, and in other embodiments at least about 80-85%, and in others greater than about 90% or more homologous or identical. A substantially homologous amino acid sequence, according to the present invention, will be encoded by a nucleic acid molecule hybridizing to SEQ ID NO: 1 or 2 or portion thereof, under stringent conditions as more particularly described above, or will be encoded by a nucleic acid molecule hybridizing to a nucleic acid sequence encoding SEQ ID NO: 3 or a portion thereof or polymorphic variant thereof, under stringent conditions as more particularly described thereof.

The invention also encompasses polypeptides having a lower degree of identity but having sufficient similarity so as to perform one or more of the same functions performed by a polypeptide encoded by a nucleic acid molecule of the invention. Similarity is determined by conserved amino acid substitution. Such substitutions are those that substitute a given amino acid in a polypeptide by another amino acid of like characteristics. Conservative substitutions are likely to be phenotypically silent. Typically seen as conservative substitutions are the replacements, one for another, among the aliphatic amino acids Ala, Val, Leu and Ile; interchange of the hydroxyl residues Ser and Thr, exchange of the acidic residues Asp and Glu, substitution between the amide residues Asn and Gln, exchange of the basic residues Lys and Arg and replacements among the aromatic residues Phe and Tyr. Guidance concerning which amino acid changes are likely to be phenotypically silent are found in Bowie *et al.*, *Science* 247:1306-1310 (1990).

A variant polypeptide can differ in amino acid sequence by one or more substitutions, deletions, insertions, inversions, fusions, and truncations or a combination of any of these. Further, variant polypeptides can be fully functional or can lack function in one or more activities. Fully functional variants typically contain only conservative variation or variation in non-critical residues or in non-critical regions. Functional variants can also contain substitution of similar amino acids that result in no change or an insignificant change in function. Alternatively, such substitutions may positively or negatively affect function to some degree. Non-functional variants typically contain one or more non-conservative amino acid substitutions, deletions, insertions, inversions, or truncation or a substitution, insertion, inversion, or deletion in a critical residue or critical region.

Amino acids that are essential for function can be identified by methods known in the art, such as site-directed mutagenesis or alanine-scanning mutagenesis (Cunningham *et al.*, *Science* 244:1081-1085 (1989)). The latter procedure introduces single alanine mutations at every residue in the molecule. The resulting mutant molecules are then tested for biological activity *in vitro*, or *in vitro* proliferative activity. Sites that are critical for polypeptide activity can also be determined by structural analysis such as crystallization, nuclear magnetic resonance or photoaffinity labeling (Smith *et al.*, *J. Mol. Biol. 224*:899-904 (1992); de Vos *et al.*, *Science 255*:306-312 (1992)).

The invention also includes fragments of the polypeptides of the invention. Fragments can be derived from a polypeptide encoded by a nucleic acid molecule comprising SEQ ID NO: 1 or 2, or the complement of SEQ ID NO: 1 or 2 (or other variants). However, the invention also encompasses fragments of the variants of the polypeptides described herein. As used herein, a fragment comprises at least 6 contiguous amino acids. Useful fragments include those that retain one or more of the biological activities of the polypeptide as well as fragments that can be used as an immunogen to generate polypeptide-specific antibodies.

Biologically active fragments (peptides which are, for example, 6, 9, 12, 15, 16, 20, 30, 35, 36, 37, 38, 39, 40, 50, 100 or more amino acids in length) can comprise

a domain, segment, or motif that has been identified by analysis of the polypeptide sequence using well-known methods, *e.g.*, signal peptides, extracellular domains, one or more transmembrane segments or loops, ligand binding regions, zinc finger domains, DNA binding domains, acylation sites, glycosylation sites, or phosphorylation sites.

Fragments can be discrete (not fused to other amino acids or polypeptides) or can be within a larger polypeptide. Further, several fragments can be comprised within a single larger polypeptide. In one embodiment a fragment designed for expression in a host can have heterologous pre- and pro-polypeptide regions fused to the amino terminus of the polypeptide fragment and an additional region fused to the carboxyl terminus of the fragment.

The invention thus provides chimeric or fusion polypeptides. These comprise a polypeptide of the invention operatively linked to a heterologous protein or polypeptide having an amino acid sequence not substantially homologous to the polypeptide. "Operatively linked" indicates that the polypeptide and the heterologous protein are fused in-frame. The heterologous protein can be fused to the N-terminus or C-terminus of the polypeptide. In one embodiment the fusion polypeptide does not affect function of the polypeptide *per se*. For example, the fusion polypeptide can be a GST-fusion polypeptide in which the polypeptide sequences are fused to the C-terminus of the GST sequences. Other types of fusion polypeptides include, but are not limited to, enzymatic fusion polypeptides, for example beta-galactosidase fusions, yeast two-hybrid GAL fusions, poly-His fusions and Ig fusions. Such fusion polypeptides, particularly poly-His fusions, can facilitate the purification of recombinant polypeptide. In certain host cells (*e.g.*, mammalian host cells), expression and/or secretion of a polypeptide can be increased using a heterologous signal sequence. Therefore, in another embodiment, the fusion polypeptide contains a heterologous signal sequence at its N-terminus.

EP-A-O 464 533 discloses fusion proteins comprising various portions of immunoglobulin constant regions. The Fc is useful in therapy and diagnosis and thus results, for example, in improved pharmacokinetic properties (EP-A 0232 262). In

drug discovery, for example, human proteins have been fused with Fc portions for the purpose of high-throughput screening assays to identify antagonists. Bennett *et al.*, *Journal of Molecular Recognition, 8*:52-58 (1995) and Johanson *et al.*, *The Journal of Biological Chemistry, 270*,16:9459-9471 (1995). Thus, this invention also encompasses soluble fusion polypeptides containing a polypeptide of the invention and various portions of the constant regions of heavy or light chains of immunoglobulins of various subclasses (IgG, IgM, IgA, IgE).

A chimeric or fusion polypeptide can be produced by standard recombinant DNA techniques. For example, DNA fragments coding for the different polypeptide sequences are ligated together in-frame in accordance with conventional techniques. In another embodiment, the fusion gene can be synthesized by conventional techniques including automated DNA synthesizers. Alternatively, PCR amplification of nucleic acid fragments can be carried out using anchor primers which give rise to complementary overhangs between two consecutive nucleic acid fragments which can subsequently be annealed and re-amplified to generate a chimeric nucleic acid sequence (see Ausubel *et al.*, *Current Protocols in Molecular Biology*, 1992). Moreover, many expression vectors are commercially available that already encode a fusion moiety (*e.g.*, a GST protein). A nucleic acid molecule encoding a polypeptide of the invention can be cloned into such an expression vector such that the fusion moiety is linked in-frame to the polypeptide.

The isolated polypeptide can be purified from cells that naturally express it, purified from cells that have been altered to express it (recombinant), or synthesized using known protein synthesis methods. In one embodiment, the polypeptide is produced by recombinant DNA techniques. For example, a nucleic acid molecule encoding the polypeptide is cloned into an expression vector, the expression vector introduced into a host cell and the polypeptide expressed in the host cell. The polypeptide can then be isolated from the cells by an appropriate purification scheme using standard protein purification techniques.

The polypeptides of the present invention can be used to raise antibodies or to elicit an immune response. The polypeptides can also be used as a reagent, *e.g.*, a

labeled reagent, in assays to quantitatively determine levels of the polypeptide or a molecule to which it binds (*e.g.*, a ligand) in biological fluids. The polypeptides can also be used as markers for cells or tissues in which the corresponding polypeptide is preferentially expressed, either constitutively, during tissue differentiation, or in diseased states. The polypeptides can be used to isolate a corresponding binding agent, *e.g.*, ligand, such as, for example, in an interaction trap assay, and to screen for peptide or small molecule antagonists or agonists of the binding interaction. For example, because members of the leukotriene pathway including LTA4H bind to receptors, the leukotriene pathway polypeptides can be used to isolate such receptors.

ANTIBODIES OF THE INVENTION

Polyclonal and/or monoclonal antibodies that specifically bind one form of the polypeptide or nucleic acid product (*e.g.*, a polypeptide encoded by a nucleic acid having a SNP as set forth in Table 3), but not to another form of the polypeptide or nucleic acid product, are also provided. Antibodies are also provided which bind a portion of either polypeptide encoded by nucleic acids of the invention (*e.g.*, SEQ ID NO: 1 or SEQ ID NO:2, or the complement of SEQ ID NO: 1 or SEQ ID NO:2), or to a polypeptide encoded by nucleic acids of the invention that contain a polymorphic site or sites. The invention also provides antibodies to the polypeptides and polypeptide fragments of the invention, or a portion thereof, or having an amino acid sequence encoded by a nucleic acid molecule comprising all or a portion of SEQ ID NOs: 1 or 2, or the complement thereof, or another variant or portion thereof. The term "antibody" as used herein refers to immunoglobulin molecules and immunologically active portions of immunoglobulin molecules, *i.e.*, molecules that contain an antigen binding site that specifically binds an antigen. A molecule that specifically binds to a polypeptide of the invention is a molecule that binds to that polypeptide or a fragment thereof, but does not substantially bind other molecules in a sample, *e.g.*, a biological sample, which naturally contains the polypeptide. Examples of immunologically active portions of immunoglobulin molecules include F(ab) and $F(ab')_2$ fragments which can be generated by treating the antibody with an enzyme

such as pepsin. The invention provides polyclonal and monoclonal antibodies that bind to a polypeptide of the invention. The term "monoclonal antibody" or "monoclonal antibody composition", as used herein, refers to a population of antibody molecules that contain only one species of an antigen binding site capable of immunoreacting with a particular epitope of a polypeptide of the invention. A monoclonal antibody composition thus typically displays a single binding affinity for a particular polypeptide of the invention with which it immunoreacts.

Polyclonal antibodies can be prepared as described above by immunizing a suitable subject with a desired immunogen, *e.g.*, polypeptide of the invention or fragment thereof. The antibody titer in the immunized subject can be monitored over time by standard techniques, such as with an enzyme linked immunosorbent assay (ELISA) using immobilized polypeptide. If desired, the antibody molecules directed against the polypeptide can be isolated from the mammal (*e.g.*, from the blood) and further purified by well-known techniques, such as protein A chromatography to obtain the IgG fraction. At an appropriate time after immunization, *e.g.*, when the antibody titers are highest, antibody-producing cells can be obtained from the subject and used to prepare monoclonal antibodies by standard techniques, such as the hybridoma technique originally described by Kohler and Milstein, *Nature* 256:495-497 (1975), the human B cell hybridoma technique (Kozbor *et al.*, *Immunol. Today* 4:72 (1983)); the EBV-hybridoma technique (Cole *et al.*, *Monoclonal Antibodies and Cancer Therapy*, Alan R. Liss, 1985, Inc., pp. 77-96); or trioma techniques. The technology for producing hybridomas is well known (see generally *Current Protocols in Immunology* (1994) Coligan *et al.* (eds.) John Wiley & Sons, Inc., New York, NY). Briefly, an immortal cell line (typically a myeloma) is fused to lymphocytes (typically splenocytes) from a mammal immunized with an immunogen as described above, and the culture supernatants of the resulting hybridoma cells are screened to identify a hybridoma producing a monoclonal antibody that binds a polypeptide of the invention.

Any of the many well known protocols used for fusing lymphocytes and immortalized cell lines can be applied for the purpose of generating a monoclonal

antibody to a polypeptide of the invention (see, *e.g.*, *Current Protocols in Immunology, supra*; Galfre *et al.*, *Nature* 266:55052 (1977); R.H. Kenneth, in *Monoclonal Antibodies: A New Dimension In Biological Analyses*, Plenum Publishing Corp., New York, New York (1980); and Lerner, *Yale J. Biol. Med.* 54:387-402 (1981). Moreover, the ordinarily skilled worker will appreciate that there are many variations of such methods that also would be useful.

Alternative to preparing monoclonal antibody-secreting hybridomas, a monoclonal antibody to a polypeptide of the invention can be identified and isolated by screening a recombinant combinatorial immunoglobulin library (*e.g.*, an antibody phage display library) with the polypeptide to thereby isolate immunoglobulin library members that bind the polypeptide. Kits for generating and screening phage display libraries are commercially available (*e.g.*, the Pharmacia *Recombinant Phage Antibody System*, Catalog No. 27-9400-01; and the Stratagene *Surf*ZAP™ Phage Display Kit, Catalog No. 240612). Additionally, examples of methods and reagents particularly amenable for use in generating and screening antibody display library can be found in, for example, U.S. Patent No. 5,223,409; PCT Publication No. WO 92/18619; PCT Publication No. WO 91/17271; PCT Publication No. WO 92/20791; PCT Publication No. WO 92/15679; PCT Publication No. WO 93/01288; PCT Publication No. WO 92/01047; PCT Publication No. WO 92/09690; PCT Publication No. WO 90/02809; Fuchs *et al.*, *Bio/Technology* 9: 1370-1372 (1991); Hay *et al.*, *Hum. Antibod. Hybridomas* 3:81-85 (1992); Huse *et al.*, *Science* 246:1275-1281 (1989); Griffiths *et al.*, *EMBO J.* 12:725-734 (1993).

Additionally, recombinant antibodies, such as chimeric and humanized monoclonal antibodies, comprising both human and non-human portions, which can be made using standard recombinant DNA techniques, are within the scope of the invention. Such chimeric and humanized monoclonal antibodies can be produced by recombinant DNA techniques known in the art.

In general, antibodies of the invention (*e.g.*, a monoclonal antibody) can be used to isolate a polypeptide of the invention by standard techniques, such as affinity chromatography or immunoprecipitation. A polypeptide-specific antibody can

facilitate the purification of natural polypeptide from cells and of recombinantly produced polypeptide expressed in host cells. Moreover, an antibody specific for a polypeptide of the invention can be used to detect the polypeptide (*e.g.*, in a cellular lysate, cell supernatant, or tissue sample) in order to evaluate the abundance and pattern of expression of the polypeptide. Antibodies can be used diagnostically to monitor protein levels in tissue as part of a clinical testing procedure, *e.g.*, to, for example, determine the efficacy of a given treatment regimen. Detection can be facilitated by coupling the antibody to a detectable substance. Examples of detectable substances include various enzymes, prosthetic groups, fluorescent materials, luminescent materials, bioluminescent materials, and radioactive materials. Examples of suitable enzymes include horseradish peroxidase, alkaline phosphatase, ß-galactosidase, or acetylcholinesterase; examples of suitable prosthetic group complexes include streptavidin/biotin and avidin/biotin; examples of suitable fluorescent materials include umbelliferone, fluorescein, fluorescein isothiocyanate, rhodamine, dichlorotriazinylamine fluorescein, dansyl chloride or phycoerythrin; an example of a luminescent material includes luminol; examples of bioluminescent materials include luciferase, luciferin and aequorin, and examples of suitable radioactive material include ^{125}I, ^{131}I, ^{35}S or ^{3}H.

As described above, antibodies to leukotrienes can be used in the methods of the invention. The methods described herein can be used to generate such antibodies for use in the methods.

DIAGNOSTIC ASSAYS

The nucleic acids, probes, primers, polypeptides and antibodies described herein can be used in methods of diagnosis of MI or diagnosis of a susceptibility to MI or to a disease or condition associated with an MI gene, such as LTA4H, as well as in kits useful for diagnosis of MI or a susceptibility to MI or to a disease or condition associated with LTA4H. In one embodiment, the kit useful for diagnosis of MI or susceptibility to MI, or to a disease or condition associated with LTA4H

comprises primers as described herein, wherein the primers contain one or more of the SNPs identified in Table 3.

In one embodiment of the invention, diagnosis of MI or susceptibility to MI (or diagnosis of or susceptibility to a disease or condition associated with LTA4H), is made by detecting a polymorphism in an LTA4H nucleic acid as described herein. The polymorphism can be an alteration in an LTA4H nucleic acid, such as the insertion or deletion of a single nucleotide, or of more than one nucleotide, resulting in a frame shift alteration; the change of at least one nucleotide, resulting in a change in the encoded amino acid; the change of at least one nucleotide, resulting in the generation of a premature stop codon; the deletion of several nucleotides, resulting in a deletion of one or more amino acids encoded by the nucleotides; the insertion of one or several nucleotides, such as by unequal recombination or gene conversion, resulting in an interruption of the coding sequence of the gene or nucleic acid; duplication of all or a part of the gene or nucleic acid; transposition of all or a part of the gene or nucleic acid; or rearrangement of all or a part of the gene or nucleic acid. More than one such alteration may be present in a single gene or nucleic acid. Such sequence changes cause an alteration in the polypeptide encoded by an LTA4H nucleic acid. For example, if the alteration is a frame shift alteration, the frame shift can result in a change in the encoded amino acids, and/or can result in the generation of a premature stop codon, causing generation of a truncated polypeptide. Alternatively, a polymorphism associated with a disease or condition associated with an LTA4H nucleic acid or a susceptibility to a disease or condition associated with an LTA4H nucleic acid can be a synonymous alteration in one or more nucleotides (*i.e.*, an alteration that does not result in a change in the polypeptide encoded by an LTA4H nucleic acid). Such a polymorphism may alter splicing sites, affect the stability or transport of mRNA, or otherwise affect the transcription or translation of the nucleic acid. An LTA4H nucleic acid that has any of the alteration described above is referred to herein as an "altered nucleic acid."

In a first method of diagnosing MI or a susceptibility to MI, hybridization methods, such as Southern analysis, Northern analysis, or *in situ* hybridizations, can

be used (see *Current Protocols in Molecular Biology*, Ausubel, F. *et al.*, eds., John Wiley & Sons, including all supplements through 1999). For example, a biological sample from a test subject (a "test sample") of genomic DNA, RNA, or cDNA, is obtained from an individual suspected of having, being susceptible to or predisposed for, or carrying a defect for, a susceptibility to a disease or condition associated with an LTA4H nucleic acid (the "test individual"). The individual can be an adult, child, or fetus. The test sample can be from any source which contains genomic DNA, such as a blood sample, sample of amniotic fluid, sample of cerebrospinal fluid, or tissue sample from skin, muscle, buccal or conjunctival mucosa, placenta, gastrointestinal tract or other organs. A test sample of DNA from fetal cells or tissue can be obtained by appropriate methods, such as by amniocentesis or chorionic villus sampling. The DNA, RNA, or cDNA sample is then examined to determine whether a polymorphism in an MI nucleic acid is present, and/or to determine which splicing variant(s) encoded by the LTA4H nucleic acid is present. The presence of the polymorphism or splicing variant(s) can be indicated by hybridization of the nucleic acid in the genomic DNA, RNA, or cDNA to a nucleic acid probe. A "nucleic acid probe", as used herein, can be a DNA probe or an RNA probe; the nucleic acid probe can contain at least one polymorphism in an LTA4H nucleic acid or contains a nucleic acid encoding a particular splicing variant of an LTA4H nucleic acid. The probe can be any of the nucleic acid molecules described above (*e.g.*, the nucleic acid, a fragment, a vector comprising the nucleic acid, a probe or primer, etc.).

To diagnose MI or a susceptibility to MI (or a disease or condition associated with LTA4H), the test sample containing an LTA4H nucleic acid is contacted with at least one nucleic acid probe to form a hybridization sample. A preferred probe for detecting mRNA or genomic DNA is a labeled nucleic acid probe capable of hybridizing to mRNA or genomic DNA sequences described herein. The nucleic acid probe can be, for example, a full-length nucleic acid molecule, or a portion thereof, such as an oligonucleotide of at least 15, 30, 50, 100, 250 or 500 nucleotides in length and sufficient to specifically hybridize under stringent conditions to appropriate mRNA or genomic DNA. For example, the nucleic acid probe can be all or a portion

of one of SEQ ID NOs: 1 or 2, or the complement thereof or a portion thereof; or can be a nucleic acid encoding all or a portion of SEQ ID NO: 3. Other suitable probes for use in the diagnostic assays of the invention are described above (see *e.g.*, probes and primers discussed under the heading, "Nucleic Acids of the Invention").

The hybridization sample is maintained under conditions that are sufficient to allow specific hybridization of the nucleic acid probe to an LTA4H nucleic acid. "Specific hybridization", as used herein, indicates exact hybridization (*e.g.*, with no mismatches). Specific hybridization can be performed under high stringency conditions or moderate stringency conditions, for example, as described above. In a particularly preferred embodiment, the hybridization conditions for specific hybridization are high stringency.

Specific hybridization, if present, is then detected using standard methods. If specific hybridization occurs between the nucleic acid probe and LTA4H nucleic acid in the test sample, then the LTA4H has the polymorphism, or is the splicing variant, that is present in the nucleic acid probe. More than one nucleic acid probe can also be used concurrently in this method. Specific hybridization of any one of the nucleic acid probes is indicative of a polymorphism in the LTA4H nucleic acid, or of the presence of a particular splicing variant encoding the LTA4H nucleic acid, and is therefore diagnostic for a disease or condition associated with LTA4H or a susceptibility to a disease or condition associated with LTA4H (*e.g.*, MI).

In Northern analysis (see *Current Protocols in Molecular Biology*, Ausubel, F. *et al.*, eds., John Wiley & Sons, *supra*) the hybridization methods described above are used to identify the presence of a polymorphism or a particular splicing variant, associated with a disease or condition associated with or a susceptibility to a disease or condition associated with LTA4H (*e.g.*, MI). For Northern analysis, a test sample of RNA is obtained from the individual by appropriate means. Specific hybridization of a nucleic acid probe, as described above, to RNA from the individual is indicative of a polymorphism in an LTA4H nucleic acid, or of the presence of a particular splicing variant encoded by an LTA4H nucleic acid, and is therefore diagnostic for

the disease or condition associated with LTA4H, or for susceptibility to a disease or condition associated with LTA4H (*e.g.*, MI).

For representative examples of use of nucleic acid probes, see, for example, U.S. Patents No. 5,288,611 and 4,851,330.

Alternatively, a peptide nucleic acid (PNA) probe can be used instead of a nucleic acid probe in the hybridization methods described above. PNA is a DNA mimic having a peptide-like, inorganic backbone, such as N-(2-aminoethyl)glycine units, with an organic base (A, G, C, T or U) attached to the glycine nitrogen via a methylene carbonyl linker (see, for example, Nielsen, P.E. *et al.*, *Bioconjugate Chemistry* 5, American Chemical Society, p. 1 (1994). The PNA probe can be designed to specifically hybridize to a nucleic acid having a polymorphism associated with a disease or condition associated with LTA4H or associated with a susceptibility to a disease or condition associated with LTA4H (*e.g.*, MI). Hybridization of the PNA probe to an LTA4H nucleic acid as described herein is diagnostic for the disease or condition or the susceptibility to the disease or condition.

In another method of the invention, mutation analysis by restriction digestion can be used to detect an altered nucleic acid, or nucleic acids containing a polymorphism(s), if the mutation or polymorphism in the nucleic acid results in the creation or elimination of a restriction site. A test sample containing genomic DNA is obtained from the individual. Polymerase chain reaction (PCR) can be used to amplify an LTA4H nucleic acid (and, if necessary, the flanking sequences) in the test sample of genomic DNA from the test individual. RFLP analysis is conducted as described (see *Current Protocols in Molecular Biology, supra*). The digestion pattern of the relevant DNA fragment indicates the presence or absence of the alteration or polymorphism in the LTA4H nucleic acid, and therefore indicates the presence or absence of a disease or condition associated with LTA4H or the susceptibility to a disease or condition associated with LTA4H (*e.g.*, MI).

Sequence analysis can also be used to detect specific polymorphisms in the LTA4H nucleic acid. A test sample of DNA or RNA is obtained from the test individual. PCR or other appropriate methods can be used to amplify the nucleic acid,

and/or its flanking sequences, if desired. The sequence of an LTA4H nucleic acid, or a fragment of the nucleic acid, or cDNA, or fragment of the cDNA, or mRNA, or fragment of the mRNA, is determined, using standard methods. The sequence of the nucleic acid, nucleic acid fragment, cDNA, cDNA fragment, mRNA, or mRNA fragment is compared with the known nucleic acid sequence of the nucleic acid, such as cDNA or MRNA (*e.g.*, one or more of SEQ ID NOs: 1 or 2, and/or the complement of SEQ ID NO: 1 or 2), or a nucleic acid sequence encoding SEQ ID NO: 3 or a fragment thereof) or other DNA, as appropriate. The presence of a polymorphism in the LTA4H nucleic acid indicates that the individual has disease or a susceptibility to a disease associated with LTA4H (*e.g.*, MI).

Allele-specific oligonucleotides can also be used to detect the presence of polymorphism(s) in the LTA4H nucleic acid, through the use of dot-blot hybridization of amplified oligonucleotides with allele-specific oligonucleotide (ASO) probes (see, for example, Saiki, R. *et al.*, *Nature* 324:163-166 (1986)). An "allele-specific oligonucleotide" (also referred to herein as an "allele-specific oligonucleotide probe") is an oligonucleotide of approximately 10-50 base pairs, for example, approximately 15-30 base pairs, that specifically hybridizes to an LTA4H nucleic acid, and that contains a polymorphism associated with a disease or condition associated with LTA4H or a susceptibility to a disease or condition associated with LTA4H (*e.g.*, MI). An allele-specific oligonucleotide probe that is specific for particular polymorphisms in an LTA4H nucleic acid can be prepared, using standard methods (see *Current Protocols in Molecular Biology*, *supra*). To identify polymorphisms in the nucleic acid associated with disease or susceptibility to disease, a test sample of DNA is obtained from the individual. PCR can be used to amplify all or a fragment of an LTA4H nucleic acid, and its flanking sequences. The DNA containing the amplified LTA4H nucleic acid (or fragment of the nucleic acid) is dot-blotted, using standard methods (see *Current Protocols in Molecular Biology*, *supra*), and the blot is contacted with the oligonucleotide probe. The presence of specific hybridization of the probe to the amplified LTA4H is then detected. Specific hybridization of an allele-specific oligonucleotide probe to DNA from the individual is indicative of a

polymorphism in the LTA4H, and is therefore indicative of a disease or condition associated with LTA4H or a susceptibility to a disease or condition associated with LTA4H (*e.g.*, MI).

An allele-specific primer hybridizes to a site on target DNA overlapping a polymorphism and only primes amplification of an allelic form to which the primer exhibits perfect complementarity. See Gibbs, *Nucleic Acid Res.* 17, 2427-2448 (1989). This primer is used in conjunction with a second primer which hybridizes at a distal site. Amplification proceeds from the two primers, resulting in a detectable product which indicates the particular allelic form is present. A control is usually performed with a second pair of primers, one of which shows a single base mismatch at the polymorphic site and the other of which exhibits perfect complementarity to a distal site. The single-base mismatch prevents amplification and no detectable product is formed. The method works best when the mismatch is included in the 3'-most position of the oligonucleotide aligned with the polymorphism because this position is most destabilizing to elongation from the primer (see, *e.g.,* WO 93/22456).

With the addition of such analogs as locked nucleic acids (LNAs), the size of primers and probes can be reduced to as few as 8 bases. LNAs are a novel class of bicyclic DNA analogs in which the 2' and 4' positions in the furanose ring are joined via an O-methylene (oxy-LNA), S-methylene (thio-LNA), or amino methylene (amino-LNA) moiety. Common to all of these LNA variants is an affinity toward complementary nucleic acids, which is by far the highest reported for a DNA analog. For example, particular all oxy-LNA nonamers have been shown to have melting temperatures of 64°C and 74°C when in complex with complementary DNA or RNA, respectively, as oposed to 28°C for both DNA and RNA for the corresponding DNA nonamer. Substantial increases in T_m are also obtained when LNA monomers are used in combination with standard DNA or RNA monomers. For primers and probes, depending on where the LNA monomers are included (*e.g.*, the 3' end, the 5'end, or in the middle), the T_m could be increased considerably.

In another embodiment, arrays of oligonucleotide probes that are complementary to target nucleic acid sequence segments from an individual, can be

used to identify polymorphisms in an LTA4H nucleic acid. For example, in one embodiment, an oligonucleotide array can be used. Oligonucleotide arrays typically comprise a plurality of different oligonucleotide probes that are coupled to a surface of a substrate in different known locations. These oligonucleotide arrays, also described as "Genechips™," have been generally described in the art, for example, U.S. Pat. No. 5,143,854 and PCT patent publication Nos. WO 90/15070 and WO 92/10092. These arrays can generally be produced using mechanical synthesis methods or light directed synthesis methods that incorporate a combination of photolithographic methods and solid phase oligonucleotide synthesis methods. See Fodor *et al.*, *Science* 251:767-777 (1991); Pirrung *et al.*, U.S. Pat. 5,143,854; (see also PCT Application WO 90/15070); Fodor *et al.*, PCT Publication WO 92/10092; and U.S. Pat. 5,424,186, the entire teachings of each of which are incorporated by reference herein. Techniques for the synthesis of these arrays using mechanical synthesis methods are described in, *e.g.*, U.S. Pat. 5,384,261, the entire teachings of which are incorporated by reference herein. In another example, linear arrays can be utilized.

Once an oligonucleotide array is prepared, a nucleic acid of interest is hybridized with the array and scanned for polymorphisms. Hybridization and scanning are generally carried out by methods described herein and also in, *e.g.*, published PCT Application Nos. WO 92/10092 and WO 95/11995, and U.S. Pat. No. 5,424,186, the entire teachings of which are incorporated by reference herein. In brief, a target nucleic acid sequence that includes one or more previously identified polymorphic markers is amplified using well-known amplification techniques, *e.g.*, PCR. Typically, this involves the use of primer sequences that are complementary to the two strands of the target sequence both upstream and downstream from the polymorphism. Asymmetric PCR techniques may also be used. Amplified target, generally incorporating a label, is then hybridized with the array under appropriate conditions. Upon completion of hybridization and washing of the array, the array is scanned to determine the position on the array to which the target sequence hybridizes. The hybridization data obtained from the scan is typically in the form of

fluorescence intensities as a function of location on the array. In a reverse method, a probe, containing a polymorphism, can be coupled to a solid surface and PCR amplicons are then added to hybridize to these probes.

Although primarily described in terms of a single detection block, *e.g.*, detection of a single polymorphism arrays can include multiple detection blocks, and thus be capable of analyzing multiple, specific polymorphisms. It will generally be understood that detection blocks may be grouped within a single array or in multiple, separate arrays so that varying, optimal conditions may be used during the hybridization of the target to the array. For example, it may often be desirable to provide for the detection of those polymorphisms that fall within G-C rich stretches of a genomic sequence, separately from those falling in A-T rich segments. This allows for the separate optimization of hybridization conditions for each situation.

Additional uses of oligonucleotide arrays for detection of polymorphisms can be found, for example, in U.S. Patents Nos. 5,858,659 and 5,837,832, the entire teachings of which are incorporated by reference herein. Other methods of nucleic acid analysis can be used to detect polymorphisms in a nucleic acid described herein, or variants encoded by a nucleic acid described herein. Representative methods include direct manual sequencing (Church and Gilbert, *Proc. Natl. Acad. Sci. USA* 81:1991-1995 (1988); Sanger, F. *et al.*, *Proc. Natl. Acad. Sci., USA* 74:5463-5467 (1977); Beavis *et al.,* U.S. Pat. No. 5,288,644); automated fluorescent sequencing; single-stranded conformation polymorphism assays (SSCP); clamped denaturing gel electrophoresis (CDGE); denaturing gradient gel electrophoresis (DGGE) (Sheffield, V.C. *et al.*, *Proc. Natl. Acad. Sci. USA* 86:232-236 (1989)), mobility shift analysis (Orita, M. *et al.*, *Proc. Natl. Acad. Sci. USA* 86:2766-2770 (1989)), restriction enzyme analysis (Flavell *et al.*, *Cell* 15:25 (1978); Geever, *et al.*, *Proc. Natl. Acad. Sci. USA* 78:5081 (1981)); heteroduplex analysis; chemical mismatch cleavage (CMC) (Cotton *et al.*, *Proc. Natl. Acad. Sci. USA* 85:4397-4401 (1985)); RNase protection assays (Myers, R.M. *et al.*, *Science* 230:1242 (1985)); use of polypeptides which recognize nucleotide mismatches, such as *E. coli* mutS protein; allele-specific PCR, for example.

In one embodiment of the invention, diagnosis of a disease or condition associated with LTA4H (*e.g.*, MI) or a susceptibility to a disease or condition associated with LTA4H (*e.g.*, MI) can also be made by expression analysis by quantitative PCR (kinetic thermal cycling). This technique utilizing TaqMan ® can be used to allow the identification of polymorphisms and whether a patient is homozygous or heterozygous. The technique can assess the presence of an alteration in the expression or composition of the polypeptide encoded by an LTA4H nucleic acid or splicing variants encoded by an LTA4H nucleic acid. Further, the expression of the variants can be quantified as physically or functionally different.

In another embodiment of the invention, diagnosis of MI or a susceptibility to MI (or of another disease or condition associated with LTA4H) can also be made by examining expression and/or composition of an LTA4H polypeptide, by a variety of methods, including enzyme linked immunosorbent assays (ELISAs), Western blots, immunoprecipitations and immunofluorescence. A test sample from an individual is assessed for the presence of an alteration in the expression and/or an alteration in composition of the polypeptide encoded by an LTA4H nucleic acid, or for the presence of a particular variant encoded by an LTA4H nucleic acid. An alteration in expression of a polypeptide encoded by an LTA4H nucleic acid can be, for example, an alteration in the quantitative polypeptide expression (*i.e.*, the amount of polypeptide produced); an alteration in the composition of a polypeptide encoded by an LTA4H nucleic acid is an alteration in the qualitative polypeptide expression (*e.g.*, expression of an altered LTA4H polypeptide or of a different splicing variant). In a preferred embodiment, diagnosis of disease or condition associated with LTA4H or a susceptibility to a disease or condition associated with LTA4H is made by detecting a particular splicing variant encoded by that LTA4H variant, or a particular pattern of splicing variants.

Both such alterations (quantitative and qualitative) can also be present. An "alteration" in the polypeptide expression or composition, refers to an alteration in expression or composition in a test sample, as compared with the expression or composition of polypeptide by an LTA4H nucleic acid in a control sample. A control

sample is a sample that corresponds to the test sample (*e.g.*, is from the same type of cells), and is from an individual who is not affected by the disease or a susceptibility to a disease or condition associated with an LTA4H nucleic acid. An alteration in the expression or composition of the polypeptide in the test sample, as compared with the control sample, is indicative of disease or condition associated with LTA4H or a susceptibility to a disease or condition associated with LTA4H (*e.g.*, MI). Similarly, the presence of one or more different splicing variants in the test sample, or the presence of significantly different amounts of different splicing variants in the test sample, as compared with the control sample, is indicative of a susceptibility to a disease or condition associated with an LTA4H nucleic acid. Various means of examining expression or composition of the polypeptide encoded by an LTA4H nucleic acid can be used, including: spectroscopy, colorimetry, electrophoresis, isoelectric focusing and immunoassays (*e.g.*, David *et al.*, U.S. Pat. 4,376,110) such as immunoblotting (see also *Current Protocols in Molecular Biology*, particularly Chapter 10). For example, in one embodiment, an antibody capable of binding to the polypeptide (*e.g.*, as described above), preferably an antibody with a detectable label, can be used. Antibodies can be polyclonal, or more preferably, monoclonal. An intact antibody, or a fragment thereof (*e.g.*, Fab or $F(ab')_2$) can be used. The term "labeled", with regard to the probe or antibody, is intended to encompass direct labeling of the probe or antibody by coupling (*i.e.*, physically linking) a detectable substance to the probe or antibody, as well as indirect labeling of the probe or antibody by reactivity with another reagent that is directly labeled. Examples of indirect labeling include detection of a primary antibody using a fluorescently labeled secondary antibody and end-labeling of a DNA probe with biotin such that it can be detected with fluorescently labeled streptavidin.

Western blotting analysis, using an antibody as described above that specifically binds to a polypeptide encoded by an altered LTA4H (*e.g.*, by an LTA4H having a SNP as shown in Table 3), or an antibody that specifically binds to a polypeptide encoded by a non-altered nucleic acid, or an antibody that specifically binds to a particular splicing variant encoded by a nucleic acid, can be used to identify

the presence in a test sample of a particular splicing variant or of a polypeptide encoded by a polymorphic or altered LTA4H, or the absence in a test sample of a particular splicing variant or of a polypeptide encoded by a non-polymorphic or non-altered nucleic acid. The presence of a polypeptide encoded by a polymorphic or altered nucleic acid, or the absence of a polypeptide encoded by a non-polymorphic or non-altered nucleic acid, is diagnostic for disease or condition associated with LTA4H or a susceptibility to a disease or condition associated with, as is the presence (or absence) of particular splicing variants encoded by the LTA4H nucleic acid.

In one embodiment of this method, the level or amount of polypeptide encoded by an LTA4H nucleic acid in a test sample is compared with the level or amount of the polypeptide encoded by the LTA4H in a control sample. A level or amount of the polypeptide in the test sample that is higher or lower than the level or amount of the polypeptide in the control sample, such that the difference is statistically significant, is indicative of an alteration in the expression of the polypeptide encoded by the LTA4H, and is diagnostic for disease or condition, or for a susceptibility to a disease or condition, associated with that LTA4H. Alternatively, the composition of the polypeptide encoded by an LTA4H nucleic acid in a test sample is compared with the composition of the polypeptide encoded by the LTA4H in a control sample (*e.g.*, the presence of different splicing variants). A difference in the composition of the polypeptide in the test sample, as compared with the composition of the polypeptide in the control sample, is diagnostic for a disease or condition, or for a susceptibility to a disease or condition, associated with that LTA4H. In another embodiment, both the level or amount and the composition of the polypeptide can be assessed in the test sample and in the control sample. A difference in the amount or level of the polypeptide in the test sample, compared to the control sample; a difference in composition in the test sample, compared to the control sample; or both a difference in the amount or level, and a difference in the composition, is indicative of a disease or condition, or a susceptibility to a disease or condition, associated with LTA4H (*e.g.*, MI).

Kits (*e.g.*, reagent kits) useful in the methods of diagnosis comprise components useful in any of the methods described herein, including for example, hybridization probes or primers as described herein (*e.g.*, labeled probes or primers), reagents for detection of labeled molecules, restriction enzymes (*e.g.*, for RFLP analysis), allele-specific oligonucleotides, antibodies which bind to altered or to non-altered (native) LTA4H polypeptide, means for amplification of nucleic acids comprising an LTA4H, or means for analyzing the nucleic acid sequence of a nucleic acid described herein, or for analyzing the amino acid sequence of a polypeptide as described herein, etc. In one embodiment, a kit for diagnosing MI or susceptibility to MI can comprise primers for nucleic acid amplification of a region in the LTA4H nucleic acid comprising an at-risk haplotype that is more frequently present in an individual having MI or susceptible to MI. The primers can be designed using portions of the nucleic acids flanking SNPs that are indicative of MI. In a particularly preferred embodiment, the primers are designed to amplify regions of the LTA4H nucleic acid associated with an at-risk haplotype for MI, as shown in Table 4 or Table 5, or more particularly the haplotype defined by the microsatellite markers and SNPs at the locus on chromosome 12q23.

SCREENING ASSAYS AND AGENTS IDENTIFIED THERBY

The invention provides methods (also referred to herein as "screening assays") for identifying the presence of a nucleotide that hybridizes to a nucleic acid of the invention, as well as for identifying the presence of a polypeptide encoded by a nucleic acid of the invention. In one embodiment, the presence (or absence) of a nucleic acid molecule of interest (*e.g.*, a nucleic acid that has significant homology with a nucleic acid of the invention) in a sample can be assessed by contacting the sample with a nucleic acid comprising a nucleic acid of the invention (*e.g.*, a nucleic acid having the sequence of one of SEQ ID NOs: 1or 2 or the complement thereof, or a nucleic acid encoding an amino acid having the sequence of SEQ ID NO: 3, or a fragment or variant of such nucleic acids), under stringent conditions as described above, and then assessing the sample for the presence (or absence) of hybridization.

In a preferred embodiment, high stringency conditions are conditions appropriate for selective hybridization. In another embodiment, a sample containing a nucleic acid molecule of interest is contacted with a nucleic acid containing a contiguous nucleic acid sequence (*e.g.*, a primer or a probe as described above) that is at least partially complementary to a part of the nucleic acid molecule of interest (*e.g.*, an LTA4H nucleic acid), and the contacted sample is assessed for the presence or absence of hybridization. In a preferred embodiment, the nucleic acid containing a contiguous nucleic acid sequence is completely complementary to a part of the nucleic acid molecule of interest.

In any of these embodiments, all or a portion of the nucleic acid of interest can be subjected to amplification prior to performing the hybridization.

In another embodiment, the presence (or absence) of a polypeptide of interest, such as a polypeptide of the invention or a fragment or variant thereof, in a sample can be assessed by contacting the sample with an antibody that specifically hybridizes to the polypeptide of interest (*e.g.*, an antibody such as those described above), and then assessing the sample for the presence (or absence) of binding of the antibody to the polypeptide of interest.

In another embodiment, the invention provides methods for identifying agents (*e.g.*, fusion proteins, polypeptides, peptidomimetics, prodrugs, receptors, binding agents, antibodies, small molecules or other drugs, or ribozymes which alter (*e.g.*, increase or decrease) the activity of the polypeptides described herein, or which otherwise interact with the polypeptides herein. For example, such agents can be agents which bind to polypeptides described herein (*e.g.*, binding agent for members of the leukotriene pathway, such as LTA4H binding agents); which have a stimulatory or inhibitory effect on, for example, activity of polypeptides of the invention; or which change (*e.g.*, enhance or inhibit) the ability of the polypeptides of the invention to interact with members of the leukotriene pathway binding agents (*e.g.*, receptors or other binding agents); or which alter posttranslational processing of the leukotriene pathway member polypeptide, such as an LTA4H polypeptide (*e.g.*, agents that alter proteolytic processing to direct the polypeptide from where it is normally synthesized

to another location in the cell, such as the cell surface; agents that alter proteolytic processing such that more polypeptide is released from the cell, etc.)

In one embodiment, the invention provides assays for screening candidate or test agents that bind to or modulate the activity of polypeptides described herein (or biologically active portion(s) thereof), as well as agents identifiable by the assays. Test agents can be obtained using any of the numerous approaches in combinatorial library methods known in the art, including: biological libraries; spatially addressable parallel solid phase or solution phase libraries; synthetic library methods requiring deconvolution; the 'one-bead one-compound' library method; and synthetic library methods using affinity chromatography selection. The biological library approach is limited to polypeptide libraries, while the other four approaches are applicable to polypeptide, non-peptide oligomer or small molecule libraries of compounds (Lam, K.S., *Anticancer Drug Des.* 12:145 (1997)).

In one embodiment, to identify agents which alter the activity of an LTA4H polypeptide, a cell, cell lysate, or solution containing or expressing an LTA4H polypeptide (*e.g.*, SEQ ID NO: 3 or another splicing variant encoded by an LTA4H nucleic acid, such as a nucleic acid comprising a SNP as shown in Table 3), or a fragment or derivative thereof (as described above), can be contacted with an agent to be tested; alternatively, the polypeptide can be contacted directly with the agent to be tested. The level (amount) of LTA4H activity is assessed (*e.g.*, the level (amount) of LTA4H activity is measured, either directly or indirectly), and is compared with the level of activity in a control (*i.e.*, the level of activity of the LTA4H polypeptide or active fragment or derivative thereof in the absence of the agent to be tested). If the level of the activity in the presence of the agent differs, by an amount that is statistically significant, from the level of the activity in the absence of the agent, then the agent is an agent that alters the activity of an LTA4H polypeptide. An increase in the level of LTA4H activity in the presence of the agent relative to the activity in the absence of the agent, indicates that the agent is an agent that enhances (stimulates) LTA4H activity. Similarly, a decrease in the level of LTA4H activity in the presence of the agent, relative to the activity in the absence of the agent, indicates that the agent

is an agent that inhibits LTA4H activity. In another embodiment, the level of activity of an LTA4H polypeptide or derivative or fragment thereof in the presence of the agent to be tested, is compared with a control level that has previously been established. A statistically significant difference in the level of the activity in the presence of the agent from the control level indicates that the agent alters LTA4H activity.

The present invention also relates to an assay for identifying agents which alter the expression of an LTA4H nucleic acid (*e.g.*, antisense nucleic acids, fusion proteins, polypeptides, peptidomimetics, prodrugs, receptors, binding agents, antibodies, small molecules or other drugs, or ribozymes); which alter (*e.g.*, increase or decrease) expression (*e.g.*, transcription or translation) of the nucleic acid or which otherwise interact with the nucleic acids described herein, as well as agents identifiable by the assays. For example, a solution containing a nucleic acid encoding an LTA4H polypeptide (*e.g.*, an LTA4H nucleic acid) can be contacted with an agent to be tested. The solution can comprise, for example, cells containing the nucleic acid or cell lysate containing the nucleic acid; alternatively, the solution can be another solution that comprises elements necessary for transcription/translation of the nucleic acid. Cells not suspended in solution can also be employed, if desired. The level and/or pattern of LTA4H expression (*e.g.*, the level and/or pattern of mRNA or of protein expressed, such as the level and/or pattern of different splicing variants) is assessed, and is compared with the level and/or pattern of expression in a control (*i.e.*, the level and/or pattern of the LTA4H expression in the absence of the agent to be tested). If the level and/or pattern in the presence of the agent differ, by an amount or in a manner that is statistically significant, from the level and/or pattern in the absence of the agent, then the agent is an agent that alters the expression of the LTA4H nucleic acid. Enhancement of LTA4H expression indicates that the agent is an activator of LTA4H transcription. Similarly, inhibition of LTA4H expression indicates that the agent is a repressor of LTA4H transcription.

In another embodiment, the level and/or pattern of LTA4H polypeptide(s) (*e.g.*, different splicing variants) in the presence of the agent to be tested, is compared

with a control level and/or pattern that have previously been established. A level and/or pattern in the presence of the agent that differs from the control level and/or pattern by an amount or in a manner that is statistically significant indicates that the agent alters LTA4H expression.

In another embodiment of the invention, agents which alter the expression of an LTA4H nucleic acid or which otherwise interact with the nucleic acids described herein, can be identified using a cell, cell lysate, or solution containing a nucleic acid encoding the promoter region of the LTA4H nucleic acid operably linked to a reporter gene. After contact with an agent to be tested, the level of expression of the reporter gene (*e.g.*, the level of mRNA or of protein expressed) is assessed, and is compared with the level of expression in a control (*i.e.*, the level of the expression of the reporter gene in the absence of the agent to be tested). If the level in the presence of the agent differs, by an amount or in a manner that is statistically significant, from the level in the absence of the agent, then the agent is an agent that alters the expression of the LTA4H nucleic acid, as indicated by its ability to alter expression of a nucleic acid that is operably linked to the LTA4H nucleic acid promoter.

Enhancement of the expression of the reporter indicates that the agent is an activator of LTA4H transcription. Similarly, inhibition of the expression of the reporter indicates that the agent is a repressor of LTA4H transcription. In another embodiment, the level of expression of the reporter in the presence of the test agent, is compared with a control level that has previously been established. A level in the presence of the agent that differs from the control level by an amount or in a manner that is statistically significant indicates that the agent alters expression.

Agents which alter the amounts of different splicing variants encoded by an LTA4H nucleic acid (*e.g.*, an agent which enhances activity of a first splicing variant, and which inhibits activity of a second splicing variant), as well as agents which are agonists of activity of a first splicing variant and antagonists of activity of a second splicing variant, can easily be identified using these methods described above.

In other embodiments of the invention, assays can be used to assess the impact of a test agent on the activity of a polypeptide relative to an LTA4H binding agent.

For example, a cell that expresses a compound that interacts with LTA4H (herein referred to as a "LTA4H binding agent", which can be a polypeptide or other molecule that interacts with LTA4H, such as a receptor, or another molecule) is contacted with LTA4H in the presence of a test agent, and the ability of the test agent to alter the interaction between LTA4H and the LTA4H binding agent is determined. Alternatively, a cell lysate or a solution containing the LTA4H binding agent, can be used. An agent which binds to LTA4H or the LTA4H binding agent can alter the interaction by interfering with, or enhancing the ability of LTA4H to bind to, associate with, or otherwise interact with the LTA4H binding agent. Determining the ability of the test agent to bind to LTA4H or an LTA4H binding agent can be accomplished, for example, by coupling the test agent with a radioisotope or enzymatic label such that binding of the test agent to the polypeptide can be determined by detecting the labeled with ^{125}I, ^{35}S, ^{14}C or ^{3}H, either directly or indirectly, and the radioisotope detected by direct counting of radioemmission or by scintillation counting. Alternatively, test agents can be enzymatically labeled with, for example, horseradish peroxidase, alkaline phosphatase, or luciferase, and the enzymatic label detected by determination of conversion of an appropriate substrate to product. It is also within the scope of this invention to determine the ability of a test agent to interact with the polypeptide without the labeling of any of the interactants. For example, a microphysiometer can be used to detect the interaction of a test agent with LTA4H or an LTA4H binding agent without the labeling of either the test agent, LTA4H, or the LTA4H binding agent. McConnell, H.M. *et al.*, *Science* 257:1906-1912 (1992). As used herein, a "microphysiometer" (*e.g.*, Cytosensor™) is an analytical instrument that measures the rate at which a cell acidifies its environment using a light-addressable potentiometric sensor (LAPS). Changes in this acidification rate can be used as an indicator of the interaction between ligand and polypeptide.

Thus, these receptors can be used to screen for compounds that are agonists for use in treating a disease or condition associated with LTA4H or a susceptibility to a disease or condition associated with LTA4H, or antagonists for studying a susceptibility to a disease or condition associated with LTA4H (*e.g.*, MI). Drugs can

be designed to regulate LTA4H activation, which in turn can be used to regulate signaling pathways and transcription events of genes downstream or of proteins or polypeptides interacting with LTA4H.

In another embodiment of the invention, assays can be used to identify polypeptides that interact with one or more LTA4H polypeptides as described herein. For example, a yeast two-hybrid system such as that described by Fields and Song (Fields, S. and Song, O., *Nature* 340:245-246 (1989)) can be used to identify polypeptides that interact with one or more LTA4H polypeptides. In such a yeast two-hybrid system, vectors are constructed based on the flexibility of a transcription factor that has two functional domains (a DNA binding domain and a transcription activation domain). If the two domains are separated but fused to two different proteins that interact with one another, transcriptional activation can be achieved, and transcription of specific markers (*e.g.*, nutritional markers such as His and Ade, or color markers such as lacZ) can be used to identify the presence of interaction and transcriptional activation. For example, in the methods of the invention, a first vector is used which includes a nucleic acid encoding a DNA binding domain and also an LTA4H polypeptide, splicing variant, or fragment or derivative thereof, and a second vector is used which includes a nucleic acid encoding a transcription activation domain and also a nucleic acid encoding a polypeptide which potentially may interact with the LTA4H polypeptide, splicing variant, or fragment or derivative thereof (*e.g.*, an LTA4H polypeptide binding agent or receptor). Incubation of yeast containing the first vector and the second vector under appropriate conditions (*e.g.*, mating conditions such as used in the Matchmaker™ system from Clontech (Palo Alto, California, USA)) allows identification of colonies that express the markers of interest. These colonies can be examined to identify the polypeptide(s) that interact with the LTA4H polypeptide or fragment or derivative thereof. Such polypeptides may be useful as agents that alter the activity of expression of an LTA4H polypeptide, as described above.

In more than one embodiment of the above assay methods of the present invention, it may be desirable to immobilize either the LTA4H, the LTA4H binding

agent, or other components of the assay on a solid support, in order to facilitate separation of complexed from uncomplexed forms of one or both of the polypeptides, as well as to accommodate automation of the assay. Binding of a test agent to the polypeptide, or interaction of the polypeptide with a binding agent in the presence and absence of a test agent, can be accomplished in any vessel suitable for containing the reactants. Examples of such vessels include microtitre plates, test tubes, and micro-centrifuge tubes. In one embodiment, a fusion protein (*e.g.*, a glutathione-S-transferase fusion protein) can be provided which adds a domain that allows LTA4H or an LTA4H binding agent to be bound to a matrix or other solid support.

In another embodiment, modulators of expression of nucleic acid molecules of the invention are identified in a method wherein a cell, cell lysate, or solution containing a nucleic acid encoding LTA4H is contacted with a test agent and the expression of appropriate mRNA or polypeptide (*e.g.*, splicing variant(s)) in the cell, cell lysate, or solution, is determined. The level of expression of appropriate mRNA or polypeptide(s) in the presence of the test agent is compared to the level of expression of mRNA or polypeptide(s) in the absence of the test agent. The test agent can then be identified as a modulator of expression based on this comparison. For example, when expression of mRNA or polypeptide is greater (statistically significantly greater) in the presence of the test agent than in its absence, the test agent is identified as a stimulator or enhancer of the mRNA or polypeptide expression. Alternatively, when expression of the mRNA or polypeptide is less (statistically significantly less) in the presence of the test agent than in its absence, the test agent is identified as an inhibitor of the mRNA or polypeptide expression. The level of mRNA or polypeptide expression in the cells can be determined by methods described herein for detecting mRNA or polypeptide.

In yet another embodiment, the invention provides methods for identifying agents (*e.g.*, fusion proteins, polypeptides, peptidomimetics, prodrugs, receptors, binding agents, antibodies, small molecules or other drugs, or ribozymes) which alter (*e.g.*, increase or decrease) the activity of a member of the leukotriene pathway binding agent, such as an LTA4H binding agent, as described herein. For example,

such agents can be agents which have a stimulatory or inhibitory effect on, for example, the activity of a member of the leukotriene pathway binding agent, such as an LTA4H binding agent; which change (*e.g.,* enhance or inhibit) the ability a member of the leukotriene pathway binding agents, (*e.g.,* receptors or other binding agents) to interact with the polypeptides of the invention; or which alter posttranslational processing of the member of the leukotriene pathway binding agent, (*e.g.,* agents that alter proteolytic processing to direct the member of the leukotriene pathway binding agent from where it is normally synthesized to another location in the cell, such as the cell surface; agents that alter proteolytic processing such that more active binding agent is released from the cell, etc.).

For example, the invention provides assays for screening candidate or test agents that bind to or modulate the activity of a member of the leukotriene pathway (or enzymatically active portion(s) thereof), as well as agents identifiable by the assays. As described above, test agents can be obtained using any of the numerous approaches in combinatorial library methods known in the art, including: biological libraries; spatially addressable parallel solid phase or solution phase libraries; synthetic library methods requiring deconvolution; the 'one-bead one-compound' library method; and synthetic library methods using affinity chromatography selection. The biological library approach is limited to polypeptide libraries, while the other four approaches are applicable to polypeptide, non-peptide oligomer or small molecule libraries of compounds (Lam, K.S. *Anticancer Drug Des., 12*:145 (1997)).

In one embodiment, to identify agents which alter the activity of a member of the leukotriene pathway (such as an LTA4H binding agent, or an agent which binds to a member of the leukotriene pathway (a "binding agent")), a cell, cell lysate, or solution containing or expressing a binding agent (*e.g.,* a leukotriene pathway member receptor, or other binding agent), or a fragment (*e.g.,* an enzymatically active fragment) or derivative thereof, can be contacted with an agent to be tested; alternatively, the binding agent (or fragment or derivative thereof) can be contacted directly with the agent to be tested. The level (amount) of binding agent activity is

assessed (either directly or indirectly), and is compared with the level of activity in a control (*i.e.*, the level of activity in the absence of the agent to be tested). If the level of the activity in the presence of the agent differs, by an amount that is statistically significant, from the level of the activity in the absence of the agent, then the agent is an agent that alters the activity of the member of the leukotriene pathway. An increase in the level of the activity relative to a control, indicates that the agent is an agent that enhances the activity. Similarly, a decrease in the level of activity relative to a control, indicates that the agent is an agent that inhibits the activity. In another embodiment, the level of activity in the presence of the agent to be tested, is compared with a control level that has previously been established. A level of the activity in the presence of the agent that differs from the control level by an amount that is statistically significant indicates that the agent alters the activity.

This invention further pertains to novel agents identified by the above-described screening assays. Accordingly, it is within the scope of this invention to further use an agent identified as described herein in an appropriate animal model. For example, an agent identified as described herein (*e.g.*, a test agent that is a modulating agent, an antisense nucleic acid molecule, a specific antibody, or a polypeptide-binding agent) can be used in an animal model to determine the efficacy, toxicity, or side effects of treatment with such an agent. Alternatively, an agent identified as described herein can be used in an animal model to determine the mechanism of action of such an agent.

Furthermore, this invention pertains to uses of novel agents identified by the above-described screening assays for treatments as described herein. In addition, an agent identified as described herein can be used to alter activity of a polypeptide encoded by an LTA4H nucleic acid, or to alter expression of an LTA4H nucleic acid, by contacting the polypeptide or the nucleic acid (or contacting a cell comprising the polypeptide or the nucleic acid) with the agent identified as described herein.

The present invention is now illustrated by the following Examples, which are not intended to be limiting in any way.

EXAMPLE 1: IDENTIFICATION OF HAPLOTYPES ASSOCIATED WITH MI

SUBJECTS AND METHODS

Study population

Patients entering the study were defined from a myocardial infarction (MI) registry that includes all MIs (over 8,000 patients) in Iceland from 1981 to 2002. This registry is a part of the World Health Organization MONICA Project (The World Health Organization MONICA Project (monitoring trends and determinants in cardiovascular disease): a major international collaboration. WHO MONICA Project Principal Investigators. *J Clin. Epidemiol.* 1988; 41:105-14). Diagnosis of all patients in the registry follow strict diagnostic rules based on symptoms, electrocardiograms, cardiac enzymes, and necropsy findings.

Blood samples from over 1500 MI patients, both cases with a family history and sporadic cases were collected. For each patient that participated, blood was collected from 2 relatives (unaffected or affected). Their genotypes were used to help with construction of haplotypes. Blood samples from over 950 controls were also collected. The control cohort was population based.

Linkage analysis

In an effort to enrich for those patients who had stronger genetic factors contributing to their risk for MI, we fractionated the MI cohort to those patients with earlier onset MI. We chose different age cutoffs for male and females since the average age of MI in females is 10 years older than for males. Using MI onset at age less than 50 in males and less than 60 in females, 196 patients were clustered within 67 Pedigrees. These pedigrees included related earlier onset MI patients such that each patient is related to at least one other patient up to and including six meiotic events. The information regarding the relatedness of patients was obtained from an encrypted genealogy database that covers the entire Icelandic nation (Gulcher *et al., Eur. J. Hum. Genet.* 8: 739-742 (2000)). A genome-wide scan was performed using a framework map of 1000 microsatellite markers, using protocols described elsewhere (Gretarsdottir S., *et al. Am. J. Hum. Genet.*,70: 593-603, 2002)). The marker order

and positions were obtained from deCODE genetic's high resolution genetic map (Kong A, *et al., Nat. genet.,* 31: 241-247 (2002)). All markers used in the linkage analysis are publicly available microsatellite markers. The population-based allele frequencies were constructed from a cohort of more than 30,000 Icelanders who have participated in genetic studies of various disease projects.

For statistical analysis, multipoint, affected only allele-sharing methods were used to assess evidence for linkage. All results, both the LOD and the non-parametric linkage (NPL) score, were obtained using the program ALLEGRO (Gudbjartsson D.F., *et al., Nat Genet.,* 25: 12-13(2000)). The baseline linkage analysis (Gretarsdottir S., *et al., Am. J. Hum. Genet.* 70: 593-603, (2002)) uses the Spairs scoring function (Whittermore AS, and Haplern J A., *Biometrics* 50: 118-127 (1994)) and Kruglyak *et al., Am. J. Hum. Genet.,* 58:1347-1363 (1996)) the exponential allele-sharing model (Kong A., and Cox N.J., *Am. J. Hum. Genet.* 61:1179-1188 (1997)), and a family weighting scheme which is halfway, on the log-scale, between weighing each affected pairs equally and weighing each family equally.

Fine mapping:

A candidate susceptibility locus was defined as the region under the LOD score curve where the score was one lower than the highest lod score ((peak lod score –1)\one lod drop). This region (approx. 12Mb) was finemapped with microsatellite markers with an average spacing between markers of approximately 1.5 cM.

Case-control haplotype association analysis

A large case-control analysis was initially carried out using over 560 male MI patients and 338 female MI patients and 480 population-based controls in an effort to find the MI gene within the linkage peak on chromosome 12 found in genome-wide linkage analysis. Given that a member of the leukotriene biosynthetic pathway, LTA4H, was near the peak microsatellite marker, an effort was made to identify microsatellite markers positioned close to, or within, the LTA4H gene. Three microsatellite markers were identified within the deCODE genetics modified

assembly of the public UCSC human genome sequence assembly and they were subsequently genotyped. In addition, SNPs were identified within the LTA4H gene by sequencing 93 patients. Out of the 90 SNPs that were identified 12 were selected to genotype 894 patients and 462 controls. These three microsatellite markers and 12 SNPs, were subsequently used for haplotype analysis. Results from the initial haplotype analysis are shown in Table 4 and Table 5.

We then typed a subset of the markers on more MI patients and controls. This subset included 8 SNPs and 3 microsatellite markers. In addition, we typed 9 new SNPs on the total cohort which now included 1560 MI patients and 953 controls. Results from the haplotype association analysis, using the extended cohort and a total of 17 SNPs and 3 microsatellite markers, are shown in Table 5.

The frequencies of haplotypes in the patient and the control groups using an expectation-maximization algorithm were estimated (Dempster A.P. *et al., J. R. Stat. Soc. B.* 39: 1-389 (1977)). An implementation of this algorithm that can handle missing genotypes and uncertainty with the phase was used. Under the null hypothesis, the patients and the controls are assumed to have identical frequencies. Using a likelihood approach, an alternative hypothesis where a candidate at-risk-haplotype is allowed to have a higher frequency in patients than controls, while the ratios of the frequencies of other haplotypes are assumed to be the same in both groups was tested. Likelihoods are maximized separately under both hypothesis and a corresponding 1-df likelihood ratio statistics is used to evaluate the statistic significance.

To assess the significance of the haplotype association corrected for multiple testing, we carried out a randomisation test using the same genotype data. We randomised the cohorts of patients and controls and repeated the analysis. This procedure was repeated up to 500 times and the adjusted P value is the fraction of replications that produced a P value for some haplotype tested that is lower than or equal to the P value we observed using the original patient and control cohorts.

Results:

Table 1 shows the results of the first step of the linkage analysis; multipoint non-parametric LOD scores for a framework marker map on chromosome 12. A LOD score suggestive of linkage of 1.95 was found at marker D12S2081. This linkage peak was one of the highest peaks found for the earlier onset MI phenotype. Table 2 shows the results of the second step of the linkage analysis; multipoint non-parametric LOD scores for the families after adding 20 fine mapping markers to the candidate region. The inclusion of additional microsatellite markers increased the information on sharing by decent from 0.8 to 0.9, around the markers that gave the highest LOD scores. The lodscore in this locus increased to 2.01 and the peak marker was D12S348 at centimorgin distance 110.6. Thus the locus remained suggestive for linkage suggesting that a gene conferring risk for MI was within the 10 million bases defined by the width of the linkage peak.

One of the genes close to the peak marker at this linkage peak (that is, the marker with the highest sharing or lodscore) was LTA4H. Our previous genetic work with FLAP showed that the leukotriene biosynthetic pathway plays a major role in MI risk. Since LTA4H encodes a major member of the leukotriene biosynthetic pathway converting Leukotriene A to Leukotriene B, we chose to test it for association to MI in a case-control study using 894 MI patients and 462 population-based controls.

Table 3 shows SNPs that were found by sequencing the LTA4H gene. One of the SNPs, LTA4H_31334, is in the coding region. The polymorphism, A\G, does not change the amino acid sequence in the protein. The rest of the SNPs were outside the coding exons of LTA4H and were within introns or flanking regions of LTA4H.

Table 4 shows results from the initial haplotype association analysis using 894 MI patients and 462 controls that were typed with 3 microsatellite markers and 12 SNPs. The following markers show a significant association with MI in males: DG12S1664, SG12S16, SG12S17, SG12S18, SG12S21, SG12S22, SG12S23, SG12S24, SG12S25, SG12S26, DG12S1666, SG12S100, SG12S28, and SG12S144, with alleles 0, C, A, T, G, G, T, T, A, T, 0, and T, T, and A, respectively. The allelic frequency of a shorter version of this haplotype including markers DG12S1664,

SG12S26, DG12S1666, and SG12S144, with alleles 0, T, 0, and A, respectively, is 51% in male MI patients and 43% in controls (carried by 76 % of male patients and 67% of controls). Allelic frequency of this haplotype is higher, or 56%, in a subgroup of patients that have had more than one MI (see Table 4).

Table 5 shows the results of the haplotype association analysis using 1560 unrelated MI patients and 953 unrelated population controls. A haplotype comprised of the consecutive markers was highly significant in MI patients that had also had either stroke or peripheral arterial occlusive disease (PAOD) (P-value adjusted for multiple comparisons = 0.007). The fact that the haplotypes shown in Table 5 are more significant in MI patients that have more than one clinically evident cardiovascular complication might indicate that the gene played a role in clinical activity or severity of the atherosclerotic disease. The significantly associated haplotype is comprised of the following consecutive markers; SG12S438, DG12S1664, SG12S16, SG12S21, SG12S23, SG12S25, SG12S26, DG12S1666, SG12S100, SG12S28, SG12S143,SG12S144, SG12S221, SG12S222, SG12S223, SG12S225, SG12S226, SG12S233, SG12S237, and DG12S1668 with alleles C, 0, C, G, T, A, T, 0, T, T, T, A, G, C, C, G, G, C,T,and 0. Also shown in Table 5 is a shorter version of the consecutive haplotype and a haplotype that shows a significant protection against MI involving more than one clinically evident cardiovascular complication.

In summary, it has been shown for the first time that genetic varians of LTA4H show significant association to MI. The results complement previous work showing that variants in FLAP are significantly associated with MI. In both cases the risk ratio is similar to or higher than the conventional and well-known risk factors for MI including smoking, hypercholesterolemia, hypertension and diabetes among others.

Table 1.

The marker map for chromosome 12 and LOD scores in the first step of the linkage analysis.

location	LOD	dhat	NPL	Zlr	Info	marker
0	1.2574	-0.4865	-1.6783	-2.4063	0.5456	D12S352
3.083	1.7993	-0.5525	-2.1441	-2.8786	0.6374	D12S1608
3.554	1.8107	-0.5494	-2.1696	-2.8877	0.6472	D12S1656
6.566	1.8434	-0.5493	-2.2066	-2.9136	0.6591	D12S1626
7.956	1.8748	-0.5527	-2.2239	-2.9383	0.6638	D12S372
12.93	1.5997	-0.4719	-2.166	-2.7142	0.7291	D12S1725
13.761	1.6842	-0.4859	-2.2249	-2.785	0.732	D12S314
16.166	1.6989	-0.5279	-2.0948	-2.7971	0.6467	D12S374
24.078	1.0258	-0.4043	-1.5861	-2.1734	0.6036	D12S336
26.254	1.0166	-0.3907	-1.6163	-2.1637	0.6338	D12S1697
31.288	0.9373	-0.3846	-1.5323	-2.0775	0.6	D12S364
34.202	0.8469	-0.3806	-1.4006	-1.9748	0.5518	D12S1728
39.399	0.8692	-0.4163	-1.3441	-2.0007	0.4871	D12S1682
44.135	0.7789	-0.3786	-1.306	-1.894	0.5121	D12S1591
49.974	0.7977	-0.3819	-1.3162	-1.9166	0.5166	D12S1640
52.254	0.8638	-0.3759	-1.4437	-1.9945	0.5749	D12S1704
53.951	0.8005	-0.3442	-1.4441	-1.92	0.6191	D12S1681
55.792	0.4155	-0.2301	-1.0815	-1.3833	0.6554	D12S345
57.468	0.2695	-0.1842	-0.8653	-1.114	0.6382	D12S1668
61.09	0.6674	-0.3134	-1.2999	-1.7531	0.6074	D12S85
67.239	0.9722	-0.3854	-1.5762	-2.116	0.6203	D12S368
74.802	0.8922	-0.3971	-1.4186	-2.027	0.5412	D12S83
76.789	0.9969	-0.4272	-1.4897	-2.1426	0.5351	D12S329
84.363	0.0618	-0.103	-0.3514	-0.5333	0.4367	D12S313
92.292	0.0266	0.052	0.2826	0.3497	0.6444	D12S326
96.995	0.2219	0.1438	0.8312	1.0108	0.6496	D12S1708
102.426	1.0345	0.2707	2.0001	2.1827	0.7615	D12S351
103.746	1.4296	0.3119	2.3732	2.5659	0.7625	D12S95
109.914	1.9537	0.3537	2.8183	2.9995	0.7796	D12S2081
112.689	1.4231	0.2984	2.4796	2.56	0.84	D12S346
114.367	1.1079	0.2685	2.1563	2.2588	0.8307	D12S1727
117.962	1.2498	0.2916	2.2133	2.3991	0.7773	D12S78
123.398	0.2995	0.1592	1.012	1.1744	0.7055	D12S1613
126.542	0.1457	0.1139	0.6968	0.819	0.6986	D12S1583
132.981	0.0058	0.0232	0.1392	0.1631	0.7222	D12S354
133.655	0.0011	0.0106	0.0607	0.0725	0.6962	D12S369
133.964	0.0012	0.0107	0.0608	0.0728	0.6913	D12S79
139.646	0.0742	0.0823	0.4953	0.5844	0.701	D12S366
142.505	0.1383	0.1088	0.694	0.7979	0.7292	D12S395

143.459	0.0732	0.0795	0.5072	0.5805	0.7417	D12S2073
143.698	0.0886	0.0875	0.5572	0.6387	0.7369	D12S1349
144.394	0.0604	0.0727	0.4591	0.5275	0.7376	D12S378
148.306	0	0.0013	0.0084	0.0096	0.7673	D12S1614
151.275	0.0125	0.0351	0.1985	0.2397	0.6764	D12S324
155.308	0.3155	0.1758	0.9568	1.2054	0.6008	D12S2075
156.144	0.2797	0.1706	0.8734	1.1348	0.5679	D12S1675
158.207	0.3194	0.1834	0.9265	1.2128	0.5549	D12S1679
162.448	0.3706	0.1872	1.0567	1.3063	0.6156	D12S1659
164.59	0.368	0.1876	1.0474	1.3019	0.6084	D12S367
172.615	0.3231	0.1872	0.9214	1.2199	0.5371	D12S1723
174.333	0.2827	0.1781	0.847	1.1411	0.5229	D12S1638

Table 2.

The marker map for chromosome 12 and LOD scores, in the second step of the linkage analysis.

location	LOD	dhat	NPL	Zlr	Info	marker
0	1.6956	-0.6253	-1.8379	-2.7944	0.4963	D12S352
3.758	2.024	-0.6098	-2.2287	-3.053	0.6154	D12S1608
4.239	2.0532	-0.6089	-2.262	-3.0749	0.6257	D12S1656
4.899	2.0351	-0.6062	-2.2476	-3.0614	0.6244	D12S100
4.949	2.0335	-0.6059	-2.2466	-3.0601	0.6243	D12S1694
5.825	1.9982	-0.5969	-2.2337	-3.0335	0.6278	D12S1615
7.41	1.895	-0.5609	-2.2259	-2.9541	0.6556	D12S1626
8.241	1.9046	-0.5627	-2.2255	-2.9616	0.6556	D12S372
9.071	1.8945	-0.5659	-2.197	-2.9537	0.6463	D12S835
9.239	1.8908	-0.5659	-2.1919	-2.9509	0.6452	D12S1050
9.628	1.8804	-0.5648	-2.1812	-2.9427	0.6435	D12S1652
13.786	1.6009	-0.4751	-2.1492	-2.7152	0.7218	D12S1725
14.624	1.596	-0.4767	-2.1379	-2.7111	0.7157	D12S314
15.679	1.7102	-0.5249	-2.1113	-2.8064	0.6569	D12S328
15.729	1.7111	-0.5255	-2.1102	-2.8071	0.656	D12S93
15.917	1.7113	-0.5272	-2.1062	-2.8073	0.6527	D12S99
16.495	1.6721	-0.5331	-2.0411	-2.7749	0.6266	D12S1673
16.684	1.6562	-0.5339	-2.0199	-2.7617	0.6192	D12S356
17.131	1.6124	-0.5336	-1.9702	-2.725	0.6035	D12S374
20.18	1.4787	-0.5541	-1.7482	-2.6095	0.5214	D12S1625
23.545	1.1182	-0.4645	-1.5402	-2.2693	0.5229	D12S397
24.869	0.9441	-0.4038	-1.4682	-2.0852	0.5568	D12S1695
24.979	0.9297	-0.3985	-1.4625	-2.0692	0.5606	D12S336
25.269	0.9337	-0.399	-1.4663	-2.0736	0.5617	D12S1674
25.559	0.9367	-0.3992	-1.4704	-2.077	0.5632	D12S1690
25.772	0.9384	-0.3989	-1.4735	-2.0788	0.5648	D12S1696

25.793	0.9385	-0.3989	-1.4738	-2.0789	0.5649	D12S77
26.767	0.9395	-0.3946	-1.4893	-2.08	0.5758	D12S827
27.155	0.937	-0.3915	-1.4961	-2.0773	0.5821	D12S1697
27.325	0.938	-0.3939	-1.4894	-2.0784	0.5766	D12S89
28.883	0.9248	-0.4057	-1.4313	-2.0636	0.5411	D12S391
30.851	0.8473	-0.39	-1.3665	-1.9754	0.5299	D12S1581
31.936	0.7765	-0.3651	-1.3345	-1.891	0.5429	D12S1580
32.188	0.7575	-0.3576	-1.3274	-1.8677	0.5489	D12S320
32.238	0.7536	-0.356	-1.326	-1.863	0.5503	D12S364
32.735	0.7445	-0.3581	-1.3038	-1.8516	0.538	D12S308
34.013	0.7073	-0.3557	-1.2478	-1.8048	0.5172	D12S2210
34.335	0.6949	-0.3532	-1.2338	-1.7889	0.5143	D12S1303
35.153	0.6582	-0.3436	-1.1984	-1.741	0.5108	D12S1728
36.074	0.693	-0.3705	-1.1841	-1.7864	0.4727	D12S1715
37.358	0.7161	-0.3917	-1.1671	-1.816	0.4445	D12S310
37.716	0.723	-0.3955	-1.1681	-1.8247	0.4414	D12S1669
39.199	0.7267	-0.3952	-1.1753	-1.8294	0.4443	D12S1650
40.35	0.7034	-0.3777	-1.1844	-1.7998	0.4644	D12S1682
45.086	0.6102	-0.3149	-1.1956	-1.6764	0.5509	D12S1591
46.757	0.645	-0.3251	-1.2237	-1.7234	0.5509	D12S1057
47.216	0.6504	-0.3287	-1.2219	-1.7307	0.5449	D12S1617
49.098	0.6565	-0.332	-1.2227	-1.7387	0.5404	D12S1596
50.007	0.6508	-0.3269	-1.2292	-1.7312	0.5503	D12S1034
50.925	0.6382	-0.3169	-1.2391	-1.7144	0.5696	D12S1640
53.204	0.7066	-0.3153	-1.3729	-1.8039	0.6362	D12S1704
53.205	0.7066	-0.3153	-1.373	-1.8039	0.6362	D12S1643
54.901	0.6809	-0.2936	-1.4087	-1.7708	0.695	D12S1681
55.526	0.5731	-0.2654	-1.301	-1.6245	0.6994	D12S1648
55.827	0.5217	-0.2504	-1.25	-1.55	0.7065	D12S61
56.499	0.4119	-0.2146	-1.1385	-1.3772	0.737	ATA73C05
56.549	0.4041	-0.2119	-1.1303	-1.3641	0.7401	D12S1621
56.793	0.3671	-0.1986	-1.0906	-1.3002	0.7572	D12S345
57.118	0.3602	-0.1959	-1.0835	-1.288	0.7615	D12S2080
58.072	0.3416	-0.1881	-1.0664	-1.2542	0.7782	D12S1048
58.469	0.3345	-0.1849	-1.0609	-1.2411	0.7867	D12S1668
59.057	0.3671	-0.1944	-1.1109	-1.3002	0.7874	D12S1589
59.716	0.4056	-0.2045	-1.1706	-1.3667	0.7932	D12S291
60.054	0.4612	-0.221	-1.2374	-1.4573	0.7826	D12S1301
61.826	0.7555	-0.2833	-1.6011	-1.8652	0.8213	D12S1713
62.09	0.7752	-0.2879	-1.6189	-1.8894	0.819	D12S85
63.701	0.8433	-0.309	-1.6549	-1.9707	0.7867	D12S1701
64.377	0.8374	-0.3088	-1.6463	-1.9637	0.7819	D12S2199
64.888	0.821	-0.3047	-1.6355	-1.9445	0.785	D12S1590
65.096	0.8096	-0.3025	-1.6239	-1.9309	0.784	D12S1627
65.665	0.8586	-0.3194	-1.6441	-1.9884	0.756	D12S1620
65.666	0.8587	-0.3194	-1.6441	-1.9885	0.7561	D12S1635

66.235	0.8957	-0.3295	-1.6678	-2.031	0.7474	D12S1633
66.236	0.8958	-0.3295	-1.6678	-2.0311	0.7473	D12S1629
66.838	0.9205	-0.3325	-1.6967	-2.0589	0.7558	D12S347
67.205	0.9208	-0.3307	-1.7028	-2.0592	0.7633	D12S1677
68.24	1.1611	-0.3656	-1.9527	-2.3124	0.8101	D12S368
68.854	1.1354	-0.3678	-1.9021	-2.2867	0.7842	D12S96
69.118	1.1237	-0.3682	-1.8815	-2.2749	0.7746	D12S398
70.315	1.0649	-0.3662	-1.7961	-2.2145	0.7407	D12S1604
70.523	1.0539	-0.3653	-1.7827	-2.2031	0.7365	D12S359
70.637	1.0579	-0.3678	-1.7787	-2.2072	0.7304	D12S1651
71.597	1.0794	-0.3844	-1.7459	-2.2296	0.6917	D12S1724
71.8	1.0813	-0.3867	-1.7392	-2.2315	0.6859	D12S1707
72.252	1.0822	-0.3904	-1.7247	-2.2324	0.6753	D12S2191
73.451	1.0636	-0.3917	-1.6882	-2.2132	0.6601	D12S1632
74.528	1.0229	-0.3828	-1.6582	-2.1704	0.6601	D12S90
74.775	1.0106	-0.3795	-1.6517	-2.1573	0.6617	D12S305
74.919	1.0029	-0.3773	-1.648	-2.1491	0.6631	D12S1298
75.69	0.9563	-0.363	-1.6289	-2.0985	0.6753	D12S1700
75.691	0.9562	-0.3629	-1.6288	-2.0984	0.6756	D12S1056
75.744	0.9527	-0.3618	-1.6276	-2.0946	0.6767	D12S1662
75.802	0.9487	-0.3605	-1.6262	-2.0902	0.6779	D12S83
75.803	0.9487	-0.3605	-1.6262	-2.0902	0.6779	D12S1655
76.339	0.9582	-0.3657	-1.6221	-2.1006	0.6682	D12S298
76.916	0.9668	-0.3701	-1.62	-2.1101	0.6606	D12S1726
77.789	0.9767	-0.3743	-1.621	-2.1209	0.6546	D12S329
80.622	0.7896	-0.3801	-1.2958	-1.9068	0.5155	D12S1649
83.513	0.4582	-0.2911	-0.9752	-1.4527	0.4746	D12S1601
84.007	0.3957	-0.2648	-0.9209	-1.35	0.4851	D12S1294
84.428	0.3441	-0.2407	-0.8746	-1.2588	0.5003	D12S335
85.558	0.2207	-0.1753	-0.75	-1.0081	0.573	D12S313
86.414	0.2075	-0.1672	-0.7361	-0.9775	0.5883	D12S375
86.588	0.2051	-0.1658	-0.7331	-0.9718	0.5905	D12S1680
87.042	0.198	-0.1615	-0.7253	-0.9549	0.5991	D12S1693
88.586	0.1683	-0.1407	-0.7008	-0.8803	0.6584	D12S1040
89.237	0.1545	-0.1303	-0.6917	-0.8436	0.6988	D12S299
89.238	0.1545	-0.1303	-0.6917	-0.8435	0.6987	D12S92
89.781	0.143	-0.1214	-0.6848	-0.8116	0.7399	D12S1052
90.368	0.131	-0.1118	-0.6779	-0.7767	0.7921	D12S337
91.289	0.155	-0.1175	-0.7641	-0.8449	0.8534	D12S1660
91.913	0.087	-0.0886	-0.5648	-0.6331	0.8225	D12S1684
92.02	0.0761	-0.0831	-0.5262	-0.5921	0.8142	D12S350
93.288	0.0009	-0.0089	-0.0583	-0.0652	0.8082	D12S326
97.989	0.2109	0.123	0.9332	0.9855	0.8597	D12S1297
97.99	0.2119	0.1234	0.9351	0.9879	0.8588	D12S106
97.991	0.213	0.1237	0.9371	0.9903	0.8578	D12S1708
99.524	0.6535	0.201	1.7426	1.7347	0.9295	D12S1667

99.525	0.6535	0.201	1.7427	1.7348	0.9296	D12S319
100.397	0.7234	0.208	1.8684	1.8252	0.9553	D12S323
100.398	0.7235	0.208	1.8686	1.8253	0.955	D12S88
100.399	0.7301	0.2091	1.8758	1.8336	0.9533	D12S1719
100.519	0.7536	0.2127	1.9016	1.8629	0.947	D12S1593
101.064	0.8567	0.2269	2.0196	1.9863	0.9341	D12S853
101.841	0.9732	0.2384	2.1747	2.117	0.951	D12S1710
102.131	1.1754	0.2589	2.4086	2.3266	0.9561	D12S1717
103.423	1.1442	0.2555	2.379	2.2955	0.9588	D12S351
104.343	1.341	0.2756	2.5694	2.485	0.9479	D12S311
104.743	1.6769	0.3035	2.8993	2.7789	0.952	D12S95
105.266	1.7384	0.3095	2.9441	2.8294	0.9441	D12S1345
106.345	1.8647	0.326	2.9793	2.9304	0.8988	D12S1346
110.627	2.0063	0.3408	3.0437	3.0397	0.8726	D12S348
110.908	1.9856	0.337	3.0533	3.0239	0.8861	D12S1716
110.909	1.9854	0.337	3.053	3.0238	0.886	D12S1657
112.477	1.3244	0.2754	2.5394	2.4696	0.9375	D12S393
112.658	1.5716	0.2988	2.7576	2.6903	0.9246	D12S1706
113.456	1.482	0.2868	2.7191	2.6125	0.9569	D12S1600
113.686	1.4654	0.2856	2.7011	2.5978	0.9556	D12S346
114.583	1.2538	0.2643	2.5203	2.4029	0.9739	D12S1641
114.628	1.2491	0.2637	2.5166	2.3984	0.9748	D12S306
114.674	1.2445	0.2632	2.5127	2.3939	0.9759	D12S332
115.043	1.3131	0.271	2.5676	2.4591	0.9635	D12S1041
115.364	1.1318	0.2546	2.3621	2.283	0.956	D12S1727
116.299	1.1829	0.2606	2.4032	2.334	0.9477	D12S1607
116.948	1.2361	0.2691	2.4273	2.3859	0.9221	IGF1
116.949	1.2361	0.2691	2.4273	2.3859	0.9219	D12S1030
117.75	1.5059	0.2956	2.6701	2.6334	0.9082	PAH
118.61	1.2001	0.2629	2.4192	2.3509	0.9435	D12S360
118.899	1.4558	0.2869	2.6729	2.5893	0.9393	D12S78
119.188	1.399	0.2838	2.5969	2.5382	0.9253	D12S338
120.067	1.3032	0.2727	2.5213	2.4498	0.943	D12S1647
120.068	1.2993	0.2723	2.5179	2.4461	0.9436	D12S317
120.348	1.4722	0.2886	2.6798	2.6038	0.9378	D12S1597
121.195	1.3839	0.2842	2.5548	2.5245	0.9127	D12S1683
124.023	0.6306	0.2003	1.693	1.7041	0.9045	D12S1342
124.297	0.6069	0.198	1.6474	1.6718	0.8927	D12S1613
125.597	0.483	0.183	1.4221	1.4915	0.8432	D12S1605
126.055	0.451	0.1786	1.3612	1.4411	0.8293	D12S84
126.796	0.3855	0.1683	1.2383	1.3324	0.8059	D12S105
127.545	0.3132	0.1527	1.1129	1.2009	0.8072	D12S1583
129.188	0.2211	0.1354	0.8864	1.009	0.7362	D12S1344
130.64	0.141	0.1122	0.6858	0.8058	0.6977	D12S1616
133.986	0.0109	0.0313	0.1941	0.2238	0.742	D12S354
134.268	0.0114	0.0321	0.1973	0.2287	0.7353	D12S1023

134.818	0.0122	0.0336	0.2027	0.237	0.7233	D12S369
134.959	0.0122	0.0336	0.2019	0.2365	0.7205	D12S1602
135.149	0.0121	0.0335	0.2006	0.2356	0.7164	D12S79
135.367	0.0102	0.0312	0.1829	0.217	0.7035	D12S1665
137.617	0.0008	0.0093	0.0498	0.0617	0.6492	D12S1718
140.815	0.0287	0.0511	0.3109	0.3633	0.7212	D12S366
141.527	0.0431	0.0638	0.374	0.4458	0.6902	D12S349
141.528	0.0879	0.0897	0.5377	0.6361	0.6935	D12S1619
141.755	0.0867	0.0892	0.5334	0.6317	0.6917	D12S385
143.676	0.0629	0.073	0.476	0.5383	0.7618	D12S395
143.677	0.0629	0.073	0.4759	0.5382	0.7615	D12S321
143.678	0.0629	0.073	0.4759	0.5381	0.7613	D12S1721
143.824	0.0588	0.0707	0.4601	0.5205	0.7614	D12S1666
144.632	0.0428	0.0604	0.3929	0.444	0.7652	D12S2073
144.962	0.0437	0.0611	0.3961	0.4485	0.7621	D12S1349
145.291	0.037	0.0563	0.3644	0.4128	0.7628	D12S1603
145.426	0.0331	0.0534	0.3446	0.3907	0.7623	D12S378
149.447	0.0134	-0.0352	-0.2159	-0.2483	0.7658	D12S1614
149.448	0.0134	-0.0352	-0.2158	-0.2483	0.7656	D12S342
152.517	0.0049	-0.0224	-0.124	-0.1505	0.6847	D12S324
153.404	0.0009	-0.0099	-0.0509	-0.064	0.6328	D12S1634
153.405	0.0009	-0.0098	-0.0507	-0.0638	0.6382	D12S307
154.88	0.0244	0.0534	0.2534	0.3353	0.561	D12S1658
155.819	0.0768	0.0941	0.447	0.5948	0.549	GATA41E12
155.94	0.0855	0.0991	0.472	0.6275	0.5489	D12S2078
157.397	0.0566	0.0832	0.3729	0.5104	0.5228	D12S1675
159.342	0.0829	0.0973	0.4654	0.6179	0.5526	D12S1679
161.157	0.1143	0.1111	0.5609	0.7255	0.5776	D12S1609
163.425	0.1165	0.1067	0.5964	0.7324	0.6407	D12S834
163.559	0.1167	0.1063	0.5993	0.733	0.6461	D12S1659
165.72	0.175	0.1287	0.7383	0.8977	0.6479	D12S1714
165.721	0.175	0.1287	0.7383	0.8978	0.648	D12S367
168.245	0.1739	0.132	0.7137	0.8949	0.6107	D12S2069
168.246	0.1739	0.132	0.7138	0.8949	0.6105	D12S97
170.298	0.2145	0.1514	0.7627	0.9938	0.5626	D12S343
170.824	0.2262	0.156	0.78	1.0207	0.5566	D12S1599
171.817	0.2496	0.1638	0.8178	1.0722	0.5531	D12S392
173.734	0.2978	0.1751	0.9099	1.171	0.5715	D12S1723
175.333	0.2667	0.1709	0.8351	1.1083	0.5393	D12S357
175.456	0.2648	0.1707	0.8307	1.1043	0.5372	D12S1638
176.211	0.2665	0.1772	0.8027	1.1079	0.4984	D12S2343

Table 3

Table 3 shows the SNPs identified within the genomic sequence, by the methods described herein. Position of the SNPs refers to SEQ ID NO 1. Sequences of the SNPs are shown in FIG. 6 or FIG. 7.

Build34 start	Build34 stop	Marker name	Marker alias	IUPAC	Public SNP	Variation	Minor allele	Minor allele %	position in Sequence
94877218	94877218	SG12S432		R	rs2270318	A/G	A	12.75	7218
94885285	94885285	SG12S438		S	rs2268517	C/G	G	9.36	15285
94896055	94896055	SG12S16	LTA4H_3645	Y		C/T	T	22.64	26055
94896115	94896115	SG12S56	LTA4H_3705	K		G/T	G	4.14	26115
94896339	94896339	SG12S57	LTA4H_3929	Y		C/T	C	2.5	26339
94896351	94896351	SG12S58	LTA4H_3941	S		C/G	C	0.85	26351
94896393	94896393	SG12S37	LTA4H_3983	W		A/T	T	9.3	26393
94896705	94896705	SG12S59	LTA4H_4295	R		A/G	A	4.5	26705
94896786	94896786	SG12S60	LTA4H_4376	R		A/G	A	2.87	26786
94896832	94896832	SG12S61	LTA4H_4422	R		A/G	G	1.56	26832
94896897	94896897	SG12S29	LTA4H_4487	W		A/T	T	4.26	26897
94896985	94896985	SG12S17	LTA4H_4575	R	rs11108372	A/G	A	41.41	26985
94897845	94897845	SG12S62	LTA4H_5435	Y		C/T	C	1.17	27845
94898878	94898878	SG12S63	LTA4H_6468	Y		C/T	T	4.46	28878
94899057	94899057	SG12S64	LTA4H_6647	Y		C/T	C	2.99	29057
94899549	94899549	SG12S18	LTA4H_7139	W		A/T	A	21.72	29549
94900318	94900318	SG12S19	LTA4H_7908	W		A/T	A	10.9	30318
94900639	94900639	SG12S65	LTA4H_8229	K		G/T	G	5.09	30639
94900892	94900892	SG12S66	LTA4H_8482	R		A/G	G	0.59	30892
94901997	94901997	SG12S68	LTA4H_9587	W		A/T	T	3.63	31997
94902169	94902169	SG12S69	LTA4H_9759	W		A/T	A	0.88	32169
94902337	94902337	SG12S70	LTA4H_9927	M		A/C	A	24.09	32337
94902454	94902454	SG12S71	LTA4H_10044	Y		C/T	C	20.93	32454
94902928	94902928	SG12S72	LTA4H_10518	Y		C/T	T	1.35	32928
94903037	94903037	SG12S30	LTA4H_10627	W	rs2540498	A/T	A	22.36	33037
94903300	94903300	SG12S73	LTA4H_10890	Y	rs2300559	C/T	C	2.33	33300
94903618	94903618	SG12S20	LTA4H_11208	M		A/C	C	39.08	33618
94903720	94903720	SG12S21	LTA4H_11310	R	rs2660880	A/G	A	5.95	33720
94905002	94905002	SG12S38	LTA4H_12592	Y	rs2110762	C/T	C	34.92	35002
94905216	94905216	SG12S74	LTA4H_12806	Y		C/T	T	0.8	35216
94905667	94905667	SG12S22	LTA4H_13257	R	rs2072510	A/G	A	36.88	35667
94905821	94905821	SG12S75	LTA4H_13411	Y		C/T	T	1.39	35821
94906078	94906078	SG12S23	LTA4H_13668	Y		C/T	C	7.06	36078
94906362	94906362	SG12S31	LTA4H_13952	Y		C/T	T	5.67	36362
94906457	94906457	SG12S76	LTA4H_14047	W	rs10492226	A/T	A	1.18	36457
94906743	94906743	SG12S77	LTA4H_14333	W		A/T	A	24.77	36743
94907375	94907375	SG12S78	LTA4H_14965	Y		C/T	T	2.48	37375
94907545	94907545	SG12S24	LTA4H_15135	Y	rs2660900	C/T	C	23.76	37545
94907935	94907935	SG12S79	LTA4H_15525	S		C/G	C	0.83	37935
94908971	94908971	SG12S32	LTA4H_16561	R	rs2540496	A/G	A	31.11	38971
94909012	94909012	SG12S80	LTA4H_16602	W		A/T	A	0.74	39012
94909191	94909191	SG12S39	LTA4H_16781	K	rs2540495	G/T	T	30.74	39191
94909554	94909554	SG12S81	LTA4H_17144	R	rs12319438	A/G	G	4.12	39554
94910164	94910164	SG12S82	LTA4H_17754	R		A/G	A	0.4	40164

94910246	94910246	SG12S83	LTA4H_17836	W		A/T	T	1.21	40246
94910273	94910273	SG12S84	LTA4H_17863	R		A/G	A	2.82	40273
94911669	94911669	SG12S25	LTA4H_19259	R	rs1978331	A/G	G	31.68	41669
94911781	94911781	SG12S85	LTA4H_19371	Y		C/T	T	1.25	41781
94914296	94914296	SG12S40	LTA4H_21886	W	rs7959337	A/T	A	5.29	44296
94916236	94916236	SG12S86	LTA4H_23826	R		A/G	G	4.71	46236
94916445	94916445	SG12S87	LTA4H_24035	Y		C/T	T	1.27	46445
94916452	94916452	SG12S88	LTA4H_24042	R	rs1990611	A/G	A	33.76	46452
94916805	94916805	SG12S89	LTA4H_24395	R	rs7981011	A/G	G	4.91	46805
94916919	94916919	SG12S26	LTA4H_24509	Y		C/T	C	17.16	46919
94917444	94917444	SG12S90	LTA4H_25034	R		A/G	A	0.84	47444
94918851	94918851	SG12S91	LTA4H_26441	Y	rs2660838	C/T	C	25	48851
94919176	94919176	SG12S92	LTA4H_26766	Y		C/T	C	20.44	49176
94919667	94919667	SG12S93	LTA4H_27257	R	rs2268516	A/G	A	2.44	49667
94920368	94920368	SG12S94	LTA4H_27958	Y	rs2660839	C/T	C	31.82	50368
94921763	94921763	SG12S41	LTA4H_29353	Y		C/T	C	20.35	51763
94921923	94921923	SG12S95	LTA4H_29513	R	rs4441106	A/G	G	7.07	51923
94922409	94922409	SG12S96	LTA4H_29999	R	rs763875	A/G	A	5.92	52409
94922502	94922502	SG12S97	LTA4H_30092	Y	rs763876	C/T	T	2.1	52502
94922681	94922681	SG12S98	LTA4H_30271	Y	rs763874	C/T	C	32.42	52681
94923446	94923446	SG12S42	LTA4H_31036	Y	rs2660892	C/T	C	27.41	53446
94923744	94923744	SG12S55	LTA4H_31334	R		A/G	A	0.27	53744
94924037	94924037	SG12S99	LTA4H_31627	R		A/G	A	4.37	54037
94924845	94924845	SG12S100	LTA4H_32435	Y	rs2247570	C/T	C	27.79	54845
94924938	94924938	SG12S101	LTA4H_32528	R		A/G	A	1.5	54938
94925915	94925915	SG12S33	LTA4H_33505	Y	rs2660895	C/T	C	30.71	55915
94926590	94926590	SG12S34	LTA4H_34180	Y	rs2247330	C/T	C	30.9	56590
94926724	94926724	SG12S102	LTA4H_34314	R	rs2247323	A/G	G	31.85	56724
94926915	94926915	SG12S103	LTA4H_34505	Y	rs2247313	C/T	T	32.74	56915
94927010	94927010	SG12S104	LTA4H_34600	Y	rs2247309	C/T	C	32.74	57010
94927133	94927133	SG12S27	LTA4H_34723	Y	rs2247304	C/T	C	25.57	57133
94927900	94927900	SG12S35	LTA4H_35490	R	rs2660897	A/G	A	35.93	57900
94927959	94927959	SG12S105	LTA4H_35549	Y	rs11108381	C/T	T	2.4	57959
94928465	94928465	SG12S28	LTA4H_36055	K	rs2660898	G/T	G	29.36	58465
94928740	94928740	SG12S36	LTA4H_36330	Y	rs2540490	C/T	T	31	58740
94928970	94928970	SG12S106	LTA4H_36560	Y	rs2540489	C/T	C	30.89	58970
94929183	94929183	SG12S107	LTA4H_36773	Y	rs11108382	C/T	T	2.58	59183
94929213	94929213	SG12S108	LTA4H_36803	R	rs2540488	A/G	A	26.28	59213
94929761	94929761	SG12S109	LTA4H_37351	Y	rs2300557	C/T	T	4.76	59761
94929770	94929770	SG12S110	LTA4H_37360	W	rs2246990	A/T	A	28.57	59770
94929936	94929936	SG12S111	LTA4H_37526	W		A/T	A	2.81	59936
94930044	94930044	SG12S112	LTA4H_37634	M		A/C	C	46.15	60044
94930343	94930343	SG12S43	LTA4H_37933	K	rs2246973	G/T	G	32.93	60343
94930357	94930357	SG12S113	LTA4H_37947	Y	rs2246972	C/T	T	33.54	60357
94931246	94931246	SG12S114	LTA4H_38836	K		G/T	T	7.55	61246
94934775	94934775	SG12S141		R	rs10777768	A/G			64775
94934975	94934975	SG12S140		M	rs2660840	A/C	C	29.77	64975
94937348	94937348	SG12S143		Y	rs2540482	C/T	C	17.02	67348
94941021	94941021	SG12S144		R	rs2660845	A/G	G	19.43	71021
94943761	94943761	SG12S221		R	rs2540475	A/G	A	16.92	73761
94946089	94946089	SG12S222		Y	rs2660850	C/T	C	15.47	76089
94948016	94948016	SG12S460		M	RS2660852	A/C	A	37.22	78016
94949965	94949965	SG12S223		Y	rs2660875	C/T	C	43.79	79965
94950568	94950568	SG12S224		R	rs2540473	A/G	G	6.12	80568

94952847	94952847	SG12S225	R	rs2540472	A/G	A	5.63	82847
94953483	94953483	SG12S226	S	rs2540471	C/G	C	37.7	83483
94953798	94953798	SG12S227	R		A/G			83798
94953801	94953801	SG12S228	Y	rs2660890	C/T	T	46.96	83801
94953831	94953831	SG12S229	M	rs2660889	A/C			83831
94954155	94954155	SG12S230	R	rs2660888	A/G	A	35.68	84155
94954449	94954449	SG12S231	Y	rs4762661	C/T			84449
94958156	94958156	SG12S232	Y		C/T			88156
94958339	94958339	SG12S233	Y	rs2660885	C/T	T	15.18	88339
94962388	94962388	SG12S234	R	rs5800242	A/G			92388
94962435	94962435	SG12S235	Y	rs759391	C/T			92435
94963320	94963320	SG12S236	S	rs2540467	C/G			93320
94963655	94963655	SG12S237	Y	rs2540466	C/T	T	37.05	93655
94963774	94963774	SG12S238	Y	rs10492225	C/T			93774
94964298	94964298	SG12S239	W	rs2660874	A/T			94298
94966584	94966584	SG12S240	W	rs2540461	A/T			96584

Table 4A. Haplotype association analysis including SNPs and microsatellite markers across the LTA4H gene.

	DG12S1664	SG12S16	SG12S17	SG12S18	SG12S21	SG12S22	SG12S23	SG12S24	SG12S25	SG12S26	DG12S1666	SG12S100	SG12S28	SG12S144	p-val	r	#aff	aff.frq.	#con	con.frq.
All MI vs controls																				
	0	C	A	T	G	G	T	T	A	T	0	T	T	A	1.67E-02	1.24	590	0.49	481	0.44
short form	0									T	0			A	3.20E-03	1.32	590	0.5	480	0.43
MI males vs controls																				
	0	C	A	T	G	G	T	T	A	T	0	T	T	A	5.10E-03	1.34	361	0.51	481	0.44
short form	0									T	0			A	1.50E-03	1.4	361	0.51	480	0.43
MI females vs controls																				
	0	C	A	T	G	G	T	T	A	T	0	T	T	A	3.80E-01	1.11	229	0.46	481	0.44
short form	0									T	0			A	1.35E-01	1.2	229	0.47	480	0.43
Recurrent MI vs controls																				
	0	C	A	T	G	G	T	T	A	T	0	T	T	A	1.50E-02	1.51	88	0.54	481	0.44
short form	0									T	0			A	2.40E-03	1.69	88	0.56	480	0.43

P-val=p-value. r=Relative risk. #aff=Number of patients. # con= number of controls. Aff.frq= haplotype/allelic frequency in patients. Con.frq= haplotype/allelic frequency in controls.

Table 4B. Information on microsatellite markers that were used in the haplotype association analysis shown in Table 4A.

Marker Name	DG12S1664
Chr	12
Cytoband	q23.1
Start in SEQ_ID_NO_1 (bp)	7855
NCBI_build33Start (Mb)	96.317853
Size	238
CEPH standard (reference allele)	245
Polymorphism type	SNP
Polymorphism class	in-del
Heterozygosity ratio	0.23
Forward primer	GGAAGGAGGACACTTCTGGA (SEQ ID NO:118)
Reverse primer	GCTGTGAATGGCTAAACTTGG (SEQ ID NO:119)

Marker Name	DG12S1666
Chr	12
Cytoband	q23.1
Start in SEQ_ID_NO_1 (bp)	38342
NCBI_build33Start (Mb)	96.34834
Size	188
CEPH standard (reference allele)	193
Polymorphism type	Microsatellite
Polymorphism class	Di
Heterozygosity ratio	0.52
Forward primer	CACAGAAGCTGCAGTGGAAG (SEQ ID NO:120)
Reverse primer	CAAATGGAGGAGTCAAGACCA (SEQ ID NO:121)

Marker Name	DG12S1668
Chr	12
Cytoband	q23.1
Start in SEQ_ID_NO_1 (bp)	86595
NCBI_build33Start (Mb)	96.396593
Size	398
CEPH standard (reference allele)	398
Polymorphism type	Microsatellite
Polymorphism class	Di
Heterozygosity ratio	0.72
Forward primer	GCAGTTTAAGCTGTATGTATATGAGG (SEQ ID NO:122)
Reverse primer	TGAAAGCCATCACTGTAAGGA (SEQ ID NO:123)

Table 5. Haplotype association analysis including SNPs and microsatellite markers in the LTA4H gene region.

	SG12S438	DG12S1664	SG12S16	SG12S21	SG12S23	SG12S25	SG12S26	DG12S1666	SG12S100	SG12S28	SG12S143	SG12S144	SG12S221	SG12S222	SG12S223	SG12S225	SG12S226	SG12S233	SG12S237	DG12S1668	p-val	P-val adj.	r	#aff	aff.frq.	#con	con.frq.
All MI vs controls																											
Consecutive	C	0	C	G	T	A	T	0	T	T	T	A	G	C	C	G	G	C	T	0	6.2E-02		1.34	1560	0.051	953	0.039
Short version	C	0												C			G			0	1.5E-03		1.63	1556	0.071	951	0.045
Protective variant	C		C				T				T								C		7.5E-02		0.88	1557	0.290	951	0.317
MI males vs controls																											
Consecutive	C	0	C	G	T	A	T	0	T	T	T	A	G	C	C	G	G	C	T	0	2.2E-02		1.49	1096	0.051	953	0.035
Short version	C	0												C			G			0	3.1E-03		1.66	1093	0.069	951	0.043
Protective variant	C		C				T				T								C		6.3E-02		0.86	1094	0.283	951	0.314
MI females vs controls																											
Consecutive	C	0	C	G	T	A	T	0	T	T	T	A	G	C	C	G	G	C	T	0	4.3E-01		1.19	464	0.046	953	0.039
Short version	C	0												C			G			0	1.6E-02		1.60	463	0.073	951	0.047
Protective variant	C		C				T				T								C		3.1E-01		0.91	463	0.301	951	0.322
Recurrent MI vs controls																											
Consecutive	C	0	C	G	T	A	T	0	T	T	T	A	G	C	C	G	G	C	T	0	7.7E-02		1.52	273	0.060	953	0.040
Short version	C	0												C			G			0	7.5E-02		1.54	272	0.067	951	0.045
Protective variant	C		C				T				T								C		9.8E-02		0.82	273	0.274	951	0.316
MI plus stroke or PAOD vs controls																											
Consecutive	C	0	C	G	T	A	T	0	T	T	T	A	G	C	C	G	G	C	T	0	1.5E-03	0.007	1.97	325	0.073	953	0.038
Short version	C	0												C			G			0	2.4E-05	0.038	2.39	325	0.099	951	0.044
Protective variant	C		C				T				T								C		4.1E-05		0.61	325	0.220	951	0.315

P-val=p-value. P-val adj: P-value adjusted for multiple comparisons. r=Relative risk. #aff=Number of patients. # con= number of controls. Aff.frq= haplotype/allelic frequency in patients. Con.frq= haplotype/allelic frequency in controls.

Discussion

In a genome wide search for susceptibility genes for MI, a gene was mapped to 12q23. This locus was fine mapped with microsatellite markers. Haplotype analysis in a large case-control association study using markers spanning a 79kb region across the LTA4H gene, shows that LTA4H is a significant susceptibility gene for MI.

The LTA4H gene encodes a protein that is required for leukotriene B4 synthesis. The leukotrienes are potent inflammatory lipid mediators derived from arachidonic acid. Given that our data shows that LTA4H shows significant association to MI, it may contribute to development of atherosclerosis in coronary arteries and/or to the destabilization of existing coronary atherosclerotic plaques through lipid oxidation and/or proinflammatory effects. In support of our discovery, Dashwood and coworkers have studied expression of the enzymes that control the formation of leukotrienes in coronary arteries. They showed that cells showing positive antibody binding to 5-LO, FLAP (5-lipoxygenase activating protein), and leukotriene A4 hydrolase were present in the coronary arteries and had a similar distribution to macrophages. *(Dashwood, et al., Circulation 1998 June 23;97(24):2406-13)*. Thus, LTA4H and other members of the leukotriene pathway are expressed within cell types found in atherosclerotic lesions that form the basis for the final event of myocardial infarction. Their potential role in plaque instability may explain why many patients have stable angina for years without suffering a myocardial infarction (and therefore presumably have atherosclerotic lesions without the instability that leads to overriding thrombosis and MI) while others suffer MI with little or no period of stable angina. Those patients with elevated LTA4H enzymatic activity in atherosclerotic lesions may have more unstable plaques and higher MI rates. In addition, increased LTA4H activity may accelerate atherosclerosis lesion formation and progression.

Our work on LTA4H is supported by our previous work on the gene that encodes FLAP, which works with 5-LO to produce Leukotriene A4; that is, it is

upstream of LTA4H. We found that variants in the FLAP gene more than double the risk of MI. LTA4H represents the second member of the leukotriene biosynthetic pathway that we have been the first to show confers substantially higher risk for MI.

Further work in animals which supports our discovery that LTA4H is a disease gene for MI comes from Aiello and coworkers. They have shown that leukotriene B4 receptor antagonism reduces monocytic foam cells in mice, suggesting that LTB4 has a role in the pathogenesis of atherosclerosis in mice. *(Aiello, et al., Arteriosclerosis, Thrombosis and Vascular Biology.* 2002;22:443.)

Finally, additional support of our human validation of the leukotriene pathways role in MI in general, and for LTA4H, in particular, comes from Mehrabian *et al.* who described the identification of 5-Lipoxygenase (5-LO) as a major gene contributing to atherosclerosis susceptibility in mice. Mehrabian *et al.* described that heterozygous deficiency for the enzyme in a knockout model decreased the atherosclerotic lesion size in LDL-/- mice by about 95%. Mehrabian *et al* show that the enzyme is expressed abundantly in macrophage-rich regions of atherosclerotic lesions, and suggested that 5-LO and/or its products might act locally to promote lesion development (Mehrabian *et al., Circulation Research.* 91:120 (2002)).

These results suggest that the Leukotriene B4 branch of the leukotriene pathway (as opposed to the other main end products of the leukotriene biosynthetic pathway: leukotriene C4, leukotriene D4, and leukotriene E4) may be more specifically involved in MI risk. If so, then medicants acting on this branch or blocking the effects of LTB4 may be more effective in preventing/treating MI than those acting on the other branches of the pathway or that block the effects of LTC4, LTD4, or LTE4. However, our current data do not exclude these other branches of the leukotriene pathway; the data do suggest that at least the LTB4 side of the leukotriene pathway is important for MI.

Mutations and /or polymorphisms within or near the LTA4H nucleic acid, and other members of the same pathway (*i.e.,* leukotriene B4 receptor 1 and 2, leukotriene B4 omega-hydroxylase, leukotriene B4 12-hydroxydehydrogenase), that show association with the disease, may be used as a diagnostic test to predict those

at risk for MI and ACS as well as those who might benefit from medicants directed against members of the leukotriene pathway. Therefore, there may be other members of the leukotriene pathway that may be valuable therapeutic targets for myocardial infarction in addition to LTA4H and FLAP.

EXAMPLE 2: MRNA EXPRESSION OF THE LTA4 HYDROLASE GENE IN WHITE BLOOD CELLS OF MI PATIENTS VS CONTROL

mRNA expression was compared in white blood cells from patients with history of myocardial infarction (MI) and in age and sex matched controls without MI. The leucocyte population was separated into: 1) neutrophils and 2) peripheral blood mononuclear cells prior to RNA extraction using standardized methods as previously described (Helgadottir *et al,* Nature Genetics, 2004; Hakonarson et al, J Immunol, 2001).

RNA was isolated from PBM cells obtainted from 43 MI patients and 35 controls. RNA was separately analyzed from granulocytes from the same subjects. Sufficient amount for RNA was obtained from all PBM cell preparations, and granulocyte preparations from 35 MI patients and 29 controls. RNA was converted into cDNA using the protocol below. PCR was then run on the cDNA with the LTA4H *Assay-on-Demand* and Beta Actin *Pre-Developed Assay Reagent* from Applied Biosystems using the PCR parameters below.

Table 6 PCR Parameters

RT Reaction

TaqMan RT Buffer	1X		
MgCl2	5.5 mM		
dNTP	0.5mM per dNTP	25°C	10'
Random Hexamers	2.5uM	48°C	30'
Rnase Inhibitor	0.4U/uL	95°C	5'
MultiScribe Reverse Transcriptase	1.25U/uL		
RNA	2ng/uL		
	50uL Reaction Volume		

PCR Reaction

TaqMan Universal Master Mix	1X	95°C	10'
TaqManAssay (20X)	1X	40 cycles:	
cDNA	2ng/ul (original RNA)	95°C	15"
	10uL Reaction Volume	60°C	60"

All PCR reactions run in duplicates.

ABI7900 instrument was used to calculate CT (Threshold Cycle) values. Samples displaying a greater than 1 deltaCT between duplicates were not used in our analysis. Quantity was obtained using the formula 2^-deltaCT where deltaCT represents the difference of CT values between target and housekeeping assay. mRNA expression was subsequently compared between patients and controls. To determine if there were differences between the groups, we used standardized Mann-Whitney analysis as well as Standard t tests, with $p<0.05$ considered significant. Moreover, given our hypothesis of enhanced expression of the LTA4 hydrolase gene in patients compared to controls, we report both unpaired two-sided and unpaired one-sided t tests with Welch correction.

Table 7 Results
Analysis

PBMC	#	# 5% extr.	Ave Q -5% extr.
Patients	43	2.15	1.954317191
Controls	35	1.75	1.72766267

Granulocytes	#	# 5% extr.	Ave Q -5% extr.
Patients	35	1.75	0.401265947
Controls	29	1.45	0.331226464

Statistics Granulocytes MI patients vs controls

P=0.0868 Mann-Whitney two-sided test

P=0.0635 Unpaired two-sided t test
P=0.0318 Unpaired one-sided t test

P=0.0556 Unpaired two-sided t test with Welch correction
P=0.0278 Unpaired one-sided t test with Welch correction

Statistics PBMC Patients vs Control

P=0.0456 Mann-Whitney two-sided test

P=0.0591 Unpaired two-sided t test
P=0.0296 Unpaired one-sided t test

P=0.0656 Unpaired two-sided t test with Welch correction
P=0.0328 Unpaired one-sided t test with Welch correction

Relative to cells isolated from control subjects, mRNA expression of LTA4 hydrolase gene is significantly enhanced in both PBM cells and granulocytes isolated from patients with MI. These data further confirmed the role of this gene in MI.

All references cited herein are incorporated by reference in their entirety. While this invention has been particularly shown and described with references to preferred embodiments thereof, it will be understood by those skilled in the art that

various changes in form and details may be made therein without departing from the scope of the invention encompassed by the appended claims.

CLAIMS

What is claimed is:

1. A method of preventing or treating myocardial infarction or decreasing susceptibility to myocardial infarction in an individual, comprising administering a leukotriene inhibitor to the individual in need thereof, in a therapeutically effective amount.

2. The method of Claim 1, wherein the individual has at least one risk factor selected from the group consisting of: an at-risk haplotype or other variant for myocardial infarction in any MI disease gene, an at-risk haplotype or variant in FLAP, an at-risk haplotype or other variant in the LTA4H gene, and a polymorphism in an LTA4H nucleic acid.

3. The method of Claim 1, wherein the individual has at least one risk factor selected from the group consisting of: diabetes; hypertension; hypercholesterolemia; elevated lp(a); obesity; and past or current smoker.

4. The method of Claim 1, wherein the individual has an elevated inflammatory marker.

5. The method of Claim 4, wherein the inflammatory marker is selected from the group consisting of: C-reactive protein (CRP), serum amyloid A, myeloperoxidase (MPO), N-tyrosine, di-tyrosine, lipoprotein phospholipase A2 (Lp-PLA2), fibrinogen, a leukotriene, a leukotriene metabolite, interleukin-6, tissue necrosis factor-alpha, a soluble vascular cell adhesion molecule (sVCAM), a soluble intervascular adhesion molecule (sICAM), E-selectin, matrix metalloprotease type-1, matrix metalloprotease type-2, matrix metalloprotease type-3, and matrix metalloprotease type-9.

6. The method of Claim 1, wherein the individual has increased total cholesterol, increased LDL cholesterol and/or decreased HDL cholesterol.

7. The method of Claim 1, wherein the individual has increased leukotriene synthesis.

8. The method of Claim 1, wherein the individual has had at least one previous myocardial infarction, ACS event, stroke, TIA or has stable angina or PAOD.

9. The method of Claim 1, wherein the individual has atherosclerosis or who requires treatment (*e.g.*, angioplasty, stents, coronary artery bypass graft) to restore blood flow in arteries.

10. The method of Claim 1, wherein the leukotriene inhibitor is selected from the group consisting of: ethyl-1-[2-[4-(phenylmethyl)phenoxy]ethyl]-4-piperidine-carboxylate, otherwise known as SC-56938; [4-[5-(3-Phenyl-propyl)thiophen-2-yl]butoxy]acetic acid, otherwise known as RP64966; (R)-S-[[4-(dimethylamino)phenyl]methyl]-N-(3-mercapto-2methyl-1-oxopropyl-L-cycteine, otherwise known as SA6541; optically pure enantiomers, salts, chemical derivatives, and analogues.

11. The method of Claim 1, wherein the leukotriene inhibitor is selected from the group consisting of LTB4 receptor antagonists as listed in the Agent Table, optically pure enantiomers, salts, chemical derivatives, and analogues.

12. The method of Claim 1, wherein the leukotriene inhibitor is an LTA4H inhibitor or antagonist.

13. The method of Claim 1, wherein the leukotriene inhibitor is a BLT1 and/or BLT2 leukotriene receptor inhibitor or antagonist.

14. The method of Claim 1, wherein the leukotriene inhibitor is a leukotriene synthesis inhibitor or antagonist, or an antibody to a leukotriene.

15. The method of Claim 1, wherein the leukotriene inhibitor is a leukotriene receptor inhibitor or antagonist.

16. The method of Claim 1, wherein the leukotriene inhibitor is an inhibitor of a member of the leukotriene LTB4 biosynthesis pathway.

17. The method of Claim 16, wherein the member of the leukotriene biosynthesis pathway is selected from the group consisting of: FLAP, 5-LO, and LTA4H.

18. A method of preventing or treating acute coronary syndrome in an individual, comprising administering a leukotriene inhibitor to the individual, in a therapeutically effective amount.

19. The method of Claim 18, wherein the acute coronary syndrome is selected from the group consisting of: unstable angina, non-ST-elevation myocardial infarction (NSTEMI) and ST-elevation myocardial infarction (STEMI).

20. The method of Claim 18, wherein the individual has at least one risk factor selected from the group consisting of: an at-risk haplotype for myocardial infarction, an at-risk haplotype in the LTA4H gene, and/or a polymorphism in an LTA4H nucleic acid.

21. The method of Claim 18, wherein the individual has at least one risk factor selected from the group consisting of: diabetes; hypertension; hypercholesterolemia; elevated lp(a); obesity; and past or current smoker.

22. The method of Claim 18, wherein the individual has an elevated inflammatory marker.

23. The method of Claim 22, wherein the inflammatory marker is selected from the group consisting of: C-reactive protein (CRP), serum amyloid A, myeloperoxidase (MPO), N-tyrosine, di-tyrosine, lipoprotein phospholipase A2 (Lp-PLA2), fibrinogen, a leukotriene, a leukotriene metabolite, interleukin-6, tissue necrosis factor-alpha, a soluble vascular cell adhesion molecule (sVCAM), a soluble intervascular adhesion molecule (sICAM), E-selectin, matrix metalloprotease type-1, matrix metalloprotease type-2, matrix metalloprotease type-3, and matrix metalloprotease type-9.

24. The method of Claim 18, wherein the individual has increased total cholesterol, increased LDL cholesterol and/or decreased HDL cholesterol.

25. The method of Claim 18, wherein the individual has increased leukotriene synthesis.

26. The method of Claim 18, wherein the individual has had at least one previous myocardial infarction or ACS event, stroke, or TIA, or has stable angina or PAOD.

27. The method of Claim 18, wherein the individual has atherosclerosis or who requires treatment (*e.g.*, angioplasty, stents, coronary artery bypass graft) to restore blood flow in arteries.

28. The method of Claim 18, wherein the leukotriene inhibitor is selected from the group consisting of: ethyl-1-[2-[4-(phenylmethyl)phenoxy]ethyl]-4-piperidine-carboxylate, otherwise known as SC-56938; [4-[5-(3-Phenyl-propyl)thiophen-2-yl]butoxy]acetic acid, otherwise known as RP64966; (R)-S-[[4-(dimethylamino)phenyl]methyl]-N-(3-mercapto-2methyl-1-oxopropyl-L-

cycteine, otherwise known as SA6541; optically pure enantiomers, salts, chemical derivatives, and analogues.

29. The method of Claim 18, wherein the leukotriene inhibitor is selected from the group consisting of LTB4 receptor antagonists as listed in the Agent Table, optically pure enantiomers, salts, chemical derivatives, and analogues.

30. The method of Claim 18, wherein the leukotriene inhibitor is an LTA4H inhibitor or antagonist.

31. The method of Claim 18, wherein the leukotriene inhibitor is a BLT1 and/or BLT2 leukotriene receptor inhibitor or antagonist.

32. The method of Claim 18, wherein the leukotriene inhibitor is a leukotriene synthesis inhibitor or antagonist, or an antibody to a leukotriene.

33. The method of Claim 18, wherein the leukotriene inhibitor is a leukotriene receptor inhibitor or antagonist.

34. The method of Claim 18, wherein the leukotriene inhibitor is an inhibitor of a member of the leukotriene LTB4 biosynthesis pathway.

35. The method of Claim 34, wherein the member of the leukotriene biosynthesis pathway is selected from the group consisting of: FLAP, 5-LO, and LTA4H.

36. A method of decreasing risk of a subsequent myocardial infarction in an individual who has had at least one myocardial infarction, comprising administering a leukotriene inhibitor to the individual, in a therapeutically effective amount.

37. The method of Claim 36, wherein the individual has at least one risk factor selected from the group consisting of: an at-risk haplotype for myocardial infarction, an at-risk haplotype in the LTA4H gene, and/or a polymorphism in an LTA4H nucleic acid.

38. The method of Claim 36, wherein the individual has at least one risk factor selected from the group consisting of: diabetes; hypertension; hypercholesterolemia; elevated lp(a); obesity; and past or current smoker.

39. The method of Claim 36, wherein the individual has an elevated inflammatory marker.

40. The method of Claim 39, wherein the inflammatory marker is selected from the group consisting of: C-reactive protein (CRP), serum amyloid A, myeloperoxidase (MPO), N-tyrosine, di-tyrosine, lipoprotein phospholipase A2 (Lp-PLA2), fibrinogen, a leukotriene, a leukotriene metabolite, interleukin-6, tissue necrosis factor-alpha, a soluble vascular cell adhesion molecule (sVCAM), a soluble intervascular adhesion molecule (sICAM), E-selectin, matrix metalloprotease type-1, matrix metalloprotease type-2, matrix metalloprotease type-3, and matrix metalloprotease type-9.

41. The method of Claim 36, wherein the individual has increased total cholesterol, increased LDL cholesterol and/or decreased HDL cholesterol.

42. The method of Claim 36, wherein the individual has increased leukotriene synthesis.

43. The method of Claim 36, wherein the individual has had at least one previous myocardial infarction or ACS event, or has stable angina.

44. The method of Claim 36, wherein the individual has atherosclerosis or who requires treatment (*e.g.*, angioplasty, stents, coronary artery bypass graft) to restore blood flow in arteries.

45. The method of Claim 36, wherein the leukotriene inhibitor is selected from the group consisting of: ethyl-1-[2-[4-(phenylmethyl)phenoxy]ethyl]-4-piperidine-carboxylate, otherwise known as SC-56938; [4-[5-(3-Phenyl-propyl)thiophen-2-yl]butoxy]acetic acid, otherwise known as RP64966; (R)-S-[[4-(dimethylamino)phenyl]methyl]-N-(3-mercapto-2methyl-1-oxopropyl-L-cycteine; otherwise known as SA6541; optically pure enantiomers, salts, chemical derivatives, and analogues.

46. The method of Claim 36, wherein the leukotriene inhibitor is selected from the group consisting of LTB4 receptor antagonists as listed in the Agent Table, optically pure enantiomers, salts, chemical derivatives, and analogues.

47. The method of Claim 36, wherein the leukotriene inhibitor is an LTA4H inhibitor or antagonist.

48. The method of Claim 36, wherein the leukotriene inhibitor is a BLT1 and/or BLT2 leukotriene receptor inhibitor or antagonist.

49. The method of Claim 36, wherein the leukotriene inhibitor is a leukotriene synthesis inhibitor or antagonist, or an antibody to a leukotriene.

50. The method of Claim 36, wherein the leukotriene inhibitor is a leukotriene receptor inhibitor or antagonist.

51. The method of Claim 36, wherein the leukotriene inhibitor is an inhibitor of a member of the leukotriene LTB4 biosynthesis pathway.

52. The method of Claim 51, wherein the member of the leukotriene biosynthesis pathway is selected from the group consisting of: FLAP, 5-LO, and LTA4H.

53. A method of treatment for atherosclerosis in an individual, comprising administering a leukotriene inhibitor to the individual, in a therapeutically effective amount.

54. The method of Claim 53, wherein the individual is concurrently treated to restore blood flow in coronary arteries.

55. The method of Claim 53, wherein the individual has at least one risk factor selected from the group consisting of: an at-risk haplotype for myocardial infarction, an at-risk haplotype in the LTA4H gene, and/or a polymorphism in an LTA4H nucleic acid.

56. The method of Claim 53, wherein the individual has at least one risk factor selected from the group consisting of: diabetes; hypertension; hypercholesterolemia; elevated lp(a); obesity; and past or current smoker.

57. The method of Claim 53, wherein the individual has an elevated inflammatory marker.

58. The method of Claim 57, wherein the inflammatory marker is selected from the group consisting of: C-reactive protein (CRP), serum amyloid A, myeloperoxidase (MPO), N-tyrosine, di-tyrosine, lipoprotein phospholipase A2 (Lp-PLA2), fibrinogen, a leukotriene, a leukotriene metabolite, interleukin-6, tissue necrosis factor-alpha, a soluble vascular cell adhesion molecule (sVCAM), a soluble intervascular adhesion molecule (sICAM), E-selectin, matrix metalloprotease type-1, matrix metalloprotease type-2, matrix metalloprotease type-3, and matrix metalloprotease type-9.

59. The method of Claim 53, wherein the individual has increased total cholesterol, increased LDL cholesterol and/or decreased HDL cholesterol.

60. The method of Claim 53, wherein the individual has increased leukotriene synthesis.

61. The method of Claim 53, wherein the individual has had at least one previous myocardial infarction or ACS event, or has stable angina.

62. The method of Claim 53, wherein the individual has atherosclerosis or who requires treatment (*e.g.*, angioplasty, stents, coronary artery bypass graft) to restore blood flow in arteries.

63. The method of Claim 53, wherein the leukotriene inhibitor is selected from the group consisting of: ethyl-1-[2-[4-(phenylmethyl)phenoxy]ethyl]-4-piperidine-carboxylate, otherwise known as SC-56938; [4-[5-(3-Phenyl-propyl)thiophen-2-yl]butoxy]acetic acid, otherwise known as RP64966; (R)-S-[[4-(dimethylamino)phenyl]methyl]-N-(3-mercapto-2methyl-1-oxopropyl-L-cycteine, otherwise known as SA6541; optically pure enantiomers, salts, chemical derivatives, and analogues.

64. The method of Claim 53, wherein the leukotriene inhibitor is selected from the group consisting of LTB4 receptor antagonists as listed in the Agent Table, optically pure enantiomers, salts, chemical derivatives, and analogues.

65. The method of Claim 53, wherein the leukotriene synthesis inhibitor is an LTA4H inhibitor or antagonist.

66. The method of Claim 53, wherein the leukotriene inhibitor is a BLT1 and/or BLT2 leukotriene receptor inhibitor or antagonist.

67. The method of Claim 53, wherein the leukotriene inhibitor is a leukotriene synthesis inhibitor or antagonist, or an antibody to a leukotriene.

68. The method of Claim 53, wherein the leukotriene inhibitor is a leukotriene receptor inhibitor or antagonist.

69. The method of Claim 53, wherein the leukotriene inhibitor is an inhibitor of a member of the leukotriene LTB4 biosynthesis pathway.

70. The method of Claim 69, wherein the member of the leukotriene biosynthesis pathway is selected from the group consisting of: FLAP, 5-LO, and LTA4H.

71. A method of antagonizing leukotriene action in an individual, comprising administering a leukotriene synthesis inhibitor or leukotriene receptor antagonist to the individual, in a therapeutically effective amount.

72. The method of Claim 71, wherein the individual is concurrently treated to restore blood flow in coronary arteries.

73. The method of Claim 71, wherein the individual has at least one risk factor selected from the group consisting of: an at-risk haplotype for myocardial infarction, an at-risk haplotype in the LTA4H gene, and/or a polymorphism in an LTA4H nucleic acid.

74. The method of Claim 71, wherein the individual has at least one risk factor selected from the group consisting of: diabetes; hypertension; hypercholesterolemia; elevated lp(a); obesity; and past or current smoker.

75. The method of Claim 71, wherein the individual has an elevated inflammatory marker.

76. The method of Claim 71, wherein the inflammatory marker is selected from the group consisting of: C-reactive protein (CRP), serum amyloid A, myeloperoxidase (MPO), N-tyrosine, di-tyrosine, lipoprotein phospholipase A2 (Lp-PLA2), fibrinogen, a leukotriene, a leukotriene metabolite, interleukin-6, tissue necrosis factor-alpha, a soluble vascular cell adhesion molecule (sVCAM), a soluble intervascular adhesion molecule (sICAM), E-selectin, matrix metalloprotease type-1, matrix metalloprotease type-2, matrix metalloprotease type-3, and matrix metalloprotease type-9.

77. The method of Claim 71, wherein the individual has increased total cholesterol, increased LDL cholesterol and/or decreased HDL cholesterol.

78. The method of Claim 71, wherein the individual has increased leukotriene synthesis.

79. The method of Claim 71, wherein the individual has had at least one previous myocardial infarction or ACS event, or has stable angina.

80. The method of Claim 71, wherein the individual has atherosclerosis or who requires treatment (*e.g.*, angioplasty, stents, coronary artery bypass graft) to restore blood flow in arteries.

81. The method of Claim 71, wherein the leukotriene synthesis inhibitor is selected from the group consisting of: ethyl-1-[2-[4-(phenylmethyl)phenoxy]ethyl]-4-piperidine-carboxylate, otherwise known as SC-56938; [4-[5-(3-Phenyl-propyl)thiophen-2-yl]butoxy]acetic acid, otherwise known as RP64966; (R)-S-[[4-(dimethylamino)phenyl]methyl]-N-(3-mercapto-2methyl-1-oxopropyl-L-cycteine, otherwise known as SA6541; optically pure enantiomers, salts, chemical derivatives, and analogues.

82. The method of Claim 71, wherein the leukotriene receptor antagonist is selected from the group consisting of LTB4 receptor antagonists as listed in the Agent Table, optically pure enantiomers, salts, chemical derivatives, and analogues.

83. The method of Claim 71, wherein the leukotriene synthesis inhibitor is an LTA4H inhibitor or antagonist.

84. The method of Claim 71, wherein the leukotriene receptor antagonist is a BLT1 and/or BLT2 leukotriene receptor inhibitor or antagonist.

85. The method of Claim 71, wherein the leukotriene synthesis inhibitor is an inhibitor of a member of the leukotriene LTB4 biosynthesis pathway.

86. The method of Claim 85, wherein the member of the leukotriene biosynthesis pathway is selected from the group consisting of: FLAP, 5-LO, and LTA4H.

87. The method of any one of Claims 1-86, wherein the leukotriene synthesis inhibitor is an agent set forth in the Agent Table or in the Additional LTA4H Agent List.

88. The method of any one of Claims 1-86, wherein the leukotriene synthesis inhibitor is an agent selected from the group consisting of: a complement of a nucleic acid encoding a member of the leukotriene pathway; a binding agent of a member of the leukotriene pathway; an agent that alters expression of a nucleic acid encoding a member of the leukotriene pathway; an agent that alters posttranslational processing of a member of the leukotriene pathway; an agent that alters activity of a polypeptide member of the leukotriene pathway; an agent that alters activity of a leukotriene; an antibody to a leukotriene; and an agent that alters interaction among two or more members of the leukotriene pathway.

89. The method of any one of Claims 1-86, wherein the leukotriene synthesis inhibitor is an agent selected from the group consisting of: an LTA4H nucleic acid binding agent; a peptidomimetic; a fusion protein; a prodrug; an antibody; an agent that alters LTA4H nucleic acid expression; an agent that alters activity of a polypeptide encoded by an LTA4H nucleic acid; an agent that alters posttranscriptional processing of a polypeptide encoded by an LTA4H nucleic acid; an agent that alters interaction of an LTA4H nucleic acid with a LTA4H nucleic acid binding agent; an agent that alters transcription of splicing variants encoded by an LTA4H nucleic acid; and ribozymes.

90. A method of assessing response to treatment with a leukotriene synthesis inhibitor, by an individual in a target population, comprising:
 a) assessing the level of leukotriene synthesis in the individual before treatment with a leukotriene synthesis inhibitor;
 b) assessing the level of leukotriene synthesis in the individual during or after treatment with the leukotriene synthesis inhibitor;
 c) comparing the level of the leukotriene before treatment with the level of the leukotriene during or after treatment,

wherein a level of the leukotriene during or after treatment that is significantly lower than the level of the leukotriene before treatment, is indicative of efficacy of treatment with the leukotriene synthesis inhibitor.

91. The method of Claim 90, wherein the level of the leukotriene in steps (a) and (b) is assessed by measurement of the leukotriene in a sample selected from the group consisting of: serum, plasma and urine.

92. The method of Claim 90, wherein the level of the leukotriene in steps (a) and (b) is assessed by measurement of *ex vivo* production of the leukotriene in a sample from the individual.

93. A method of assessing response to treatment with a leukotriene inhibitor, by an individual in a target population, comprising:
   a) assessing the level of an inflammatory marker in the individual before treatment with a leukotriene inhibitor
   b) assessing the level of the inflammatory marker in the individual during or after treatment with the leukotriene inhibitor;
   c) comparing the level of the inflammatory marker before treatment with the level of the inflammatory marker during or after treatment,

   wherein a level of the inflammatory marker during or after treatment that is significantly lower than the level of inflammatory marker before treatment, is indicative of efficacy of treatment with the leukotriene inhibitor.

94. The method of Claim 93, wherein the inflammatory marker is selected from the group consisting of: C-reactive protein (CRP), serum amyloid A, myeloperoxidase (MPO), N-tyrosine, di-tyrosine, lipoprotein phospholipase A2 (Lp-PLA2), fibrinogen, a leukotriene, a leukotriene metabolite (*e.g.*, cysteinyl leukotrienes), interleukin-6, tissue necrosis factor-alpha, soluble vascular cell adhesion molecules (sVCAM), soluble intervascular adhesion molecules (sICAM), E-selectin, matrix metalloprotease type-1, matrix metalloprotease type-2, matrix metalloprotease type-3, and matrix metalloprotease type-9.

95. A method of diagnosing susceptibility to MI or ACS in an individual, comprising screening for an at-risk haplotype in the LTA4H gene that is more frequently present in an individual susceptible to MI or ACS compared to the frequency of its presence in a healthy individual, wherein the at-risk haplotype increases risk of MI or ACS significantly.

96. The method of claim 95 wherein the significant increase is at least about 20%.

97. The method of claim 95 wherein the significant increase is identified as an odds ratio of at least about 1.2.

98. A method of diagnosing susceptibility to a MI or ACS in an individual, comprising screening for an at-risk haplotype in the LTA4H gene that is more frequently present in an individual susceptible to MI or ACS compared to the frequency of its presence in a healthy individual, wherein the presence of the at-risk haplotype.is indicative of a susceptibility to MI or ACS.

99. A method of diagnosing susceptibility to MI or ACS in an individual, comprising screening for the presence of an at-risk haplotype within or near the LTA4H gene that is more frequently present in an individual susceptible to MI or ACS compared to the frequency of its presence in a healthy individual, wherein the at-risk haplotype significantly correlates with susceptibility to MI or ACS.

100. The method of Claim 99, wherein the at-risk haplotype within or near LTA4H comprises makers DG12S1664, SG12S26, DG12S1666, and SG12S144, with alleles 0, T, 0, and A, respectively.

101. A method of diagnosing susceptibility to MI or ACS in an individual, comprising assessing a sample from the individual for the presence of tagging markers in a haplotype block comprising the LTA4H gene, wherein the presence of tagging markers in the haplotype block that are more frequently present in an individual susceptible to MI or ACS (affected), compared to the frequency of its presence in a healthy individual (control), wherein the presence of the tagging markers is indicative of a susceptibility to MI or ACS.

102. A method of diagnosing a susceptibility to MI or ACS in an individual, comprising detecting one or more markers at one or more polymorphic sites,

wherein the one or more polymomrphic sites are in linkage disequilibrium with a marker within or near LTA4H.

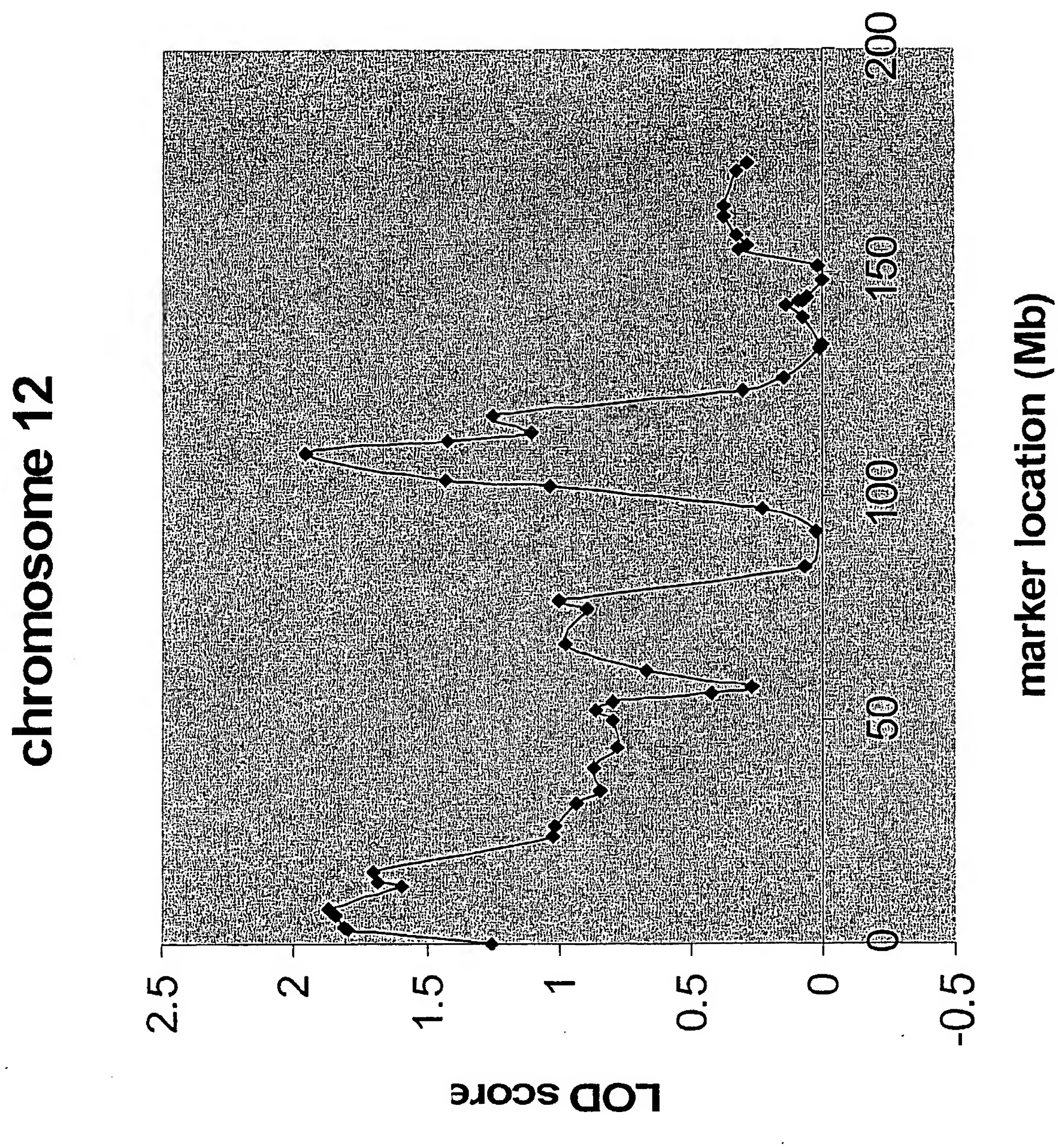
chromosome 12
LOD score
marker location (Mb)
2.5
2
1.5
1
0.5
0
-0.5
0
50
100
150
200

FIG. 1

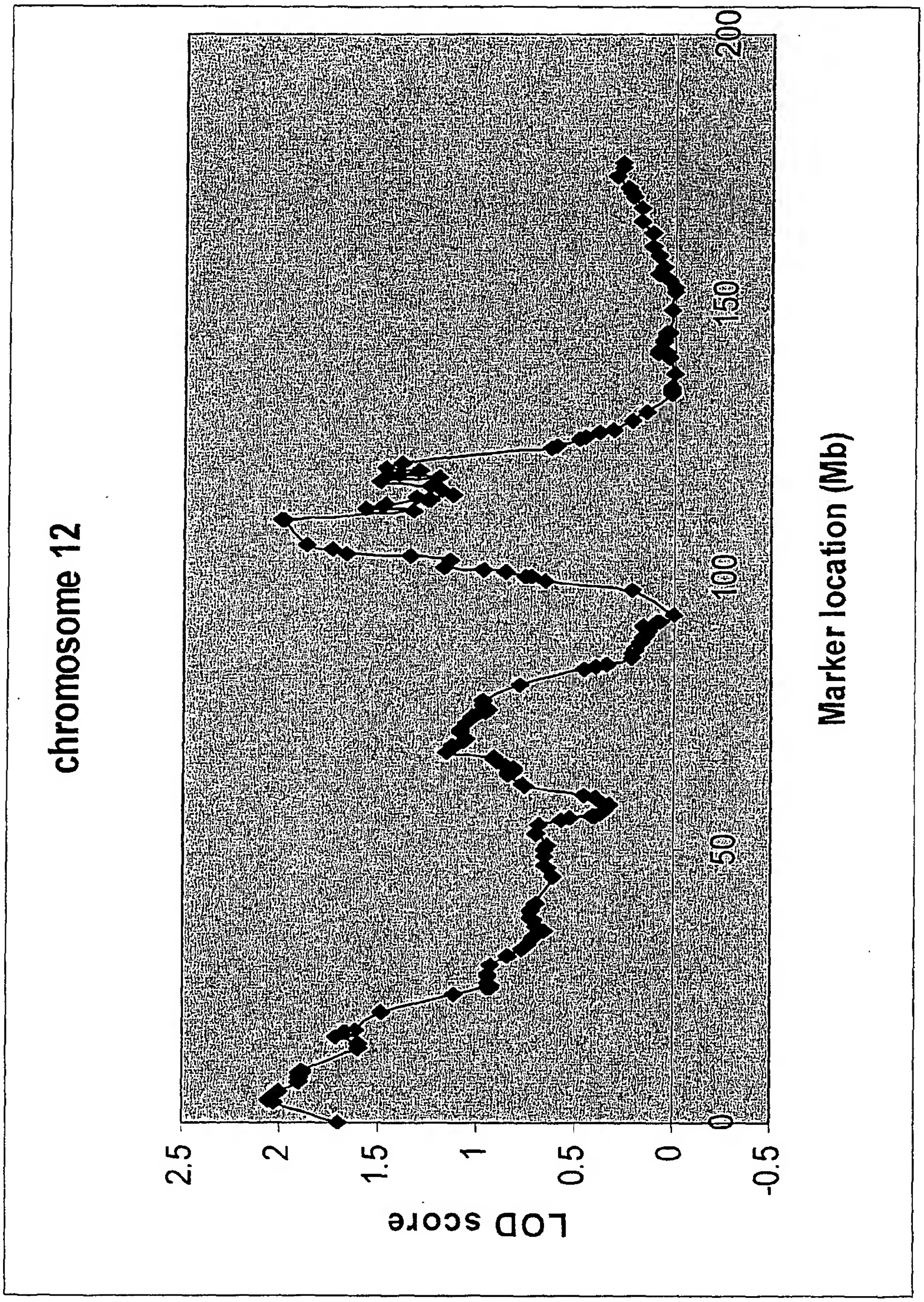
chromosome 12
LOD score
2.5
2
1.5
1
0.5
0
-0.5
0
50
100
150
200
Marker location (Mb)

FIG. 2

>Homo_sapiens:Build34:chr12:94870000..94970000+
TAAGGCATATCATGCAAAGTAAAATTAGCCAAAGAAAGTCAACTGGTGGA
GAGCTTGTTGAAGCaaatttaaaaaaaaaaaaaaGGTTAACAAAAGTCT
AATGTTTTTAGAAAAAATTGCTATCAATCTGTTTCCAAATTTGAATTCAT
CTAATGCTAAGAGTAAAAAACAGGCACATACAATTGTGGTTATTCTTCTC
ACCCTTAAGAGTGAGTGGCCTGTTGAAACTGTTAAGAAAGAAAGAAAAGT
TTTATAATCTGAAAATACCTGGTGGGTCTTGAACCACGACAACAGGAACA
CAGTGCTGAATTTAGCAACTATAATACTGCCATCAGCCTAACCAACGTAG
GCTTTAGAAGAACTGAATGATACAATGGATTGATCTACCTAGGAAAGTTC
TCAGGTCTCTCCTTCAGCCTAGTATTGCTTTGTGCTAAACTGACTGCCCT
CTCATCTGCTACTTCATGACAAAGCCCATTAAAGGTCCTCAGACTCCGGG
ATTTTGGTGGATTTCTTGTGCAGAAATTGCAGTGAAAAGGCTGTTGGAGA
AAGAGGTCTTGATTCTGGAATATGCTCCATTCTGTATTTTTCAATGTATG
GAGCAGCTACTTCCCAAACCTGAAAAGCAAGGACAAAACAAAGTTGAAAT
ATTGACGACATTGTTTCCACATGCTATTAAACATCAACTTCATCCGAAGT
CAAAACATACTCTATACATGACCAGACACAGCTGCTGTTTGCTTGCTTTT
ATTTTAAGCCATTTGACACATGACCTGTGTCAATTAGTCTTTGGTTGCAT
TAAAGACTGTAAATATACAAAGTCCAAAACTTTCTAAAGTCATCATAAAG
ATTTTAAGCTGCATACTTTTCCTAAGCAAAACAAGCAAGCAAATAACAAA
ACCCAGAGAATTCAGTGTGGATAGAGTGAAGGATAGTTGCTCCAGGGTCT
TAACAGTACCTATGTGGTTTTTTTCttgtttttttgtttttttcttttt
ttgtgagacagagtctcactctgtcgcccaggctggagtgcagtagcatg
atctcagctcactgcaacctccaccttccaggttcaagcaattcttgtgc
ctcagcctcctgagtagctgggattacaggtgcatgccaccaggcccagc
taatttttgtatttttagcagagatggggtttcaccatgttggccaggct
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TTCTAAAGCAAGCCTTAAATGGTAAAAGGCAGTGAATTGTATTTCCCTAT
TGCCTTATTTCCATGCCACAGGTGCTCTGTTCCTTTGACCCtgctactca
aagcgtggcctgtgcccctgcagtatcagcatcacctgggacaagtcaga
atcttggccttcacccagacctactgaatccacacctgcattttaacaag
atgcccagcagattcatagccactttaatgttggagaggcaCTGCCTCAG
ATCCTTGGTTAGCTTTTGCCTCCCACCCACCAACCTCtttttttcttttttt
tttttttttcttAAGCATAACATCATCTCAAAGTAAGGCCCTGGAcgggc
atggtggcatgtgcctgtagtcccagctactcaagaagccaaagtgggag
gatcacttgagcccaggagtttgagtccagccttggcaacatagcaagac
ccgcatctctaaaaaaaTTTTTTTTTAAATTGAATGAAATTAAGGCCCTG
TTTTTGGTTTATATCTGCTTTTTAACTGATTGCCACTGACAGCCAAGGAG
CCTTTCCTATTATTTTTTATGACCTTAGCAAATGAATACTCTTAAAGGCT
AACCTCTCGTATACCTCCCTCCTAGCACCAAAGTTGGCAGCAGGCAAGCA
GCTTCCCCATCCAGAGTGCAGGGCATGCTTAGAAATAATGGGTGTGAAAA
TCACAGGGAAAAATCACTGCCCCAGAGCAGAGCAACTGTTTTAAGGAAAT
CAAGCGATTCTAGGGAACATAACACCCACAAGTTATTCAAAAGGTTTAAA
GCACTTCAAAAACGATATTTAAAAGATAAGCCAGCATGCTGGGCATCTGT
ACCTGGCAGCTGAGTATACGGTCAATGTAACCAGTGGAAATATGCAAGAA
AGAAAAACCCGCATCTCACCAGAGCACTAGACAGACCGAAAGTCTTCTGA
AGTAAACACCCGGGCCTTGGTTTTCTCTCCAGGTCTACGCAGCCATTGCA
CCCAGTGGTGGTAGTTGTGATAGCATCACCCAGAAGGGAACGCACTTTTG
AATCAAAGAGGACATCTTGCAGGGGTGGGGAGGCATCAATGAACCTGACA
TCTTATTTTTTTCCCCATGAATATTGTCCCAAAACTCCATTTAAAATCCA
TTTCTGTTTCTAATCCTTAGATATTCAACCGTTGGCTGCACCCTGGTGCA
CTTAGTGTTTATTATATGGCTTCTTAGTGGTGCTGCAAGTTGTTGCTCAA
ATACCTTTTTGCTCATTCCCAAGGAATGGCCAGAAAACAATAGAATAAGG
CAATGTTTCTCCATCCCCGACTTTGCTTTCCTGTAACAATTAAAAATTAA
GAAACAAGCCAAGGAGCCAGCTTGCCTTCTGCTCCAGGAGCAGCCTGTGG
GCTGCCTCGATGTCCGGGGCCATGAAGCGATCTTTATCCAGGGCCTACA
GGGAGAGCACATCCGCCCATCAGCCAAACATGAAACCCTGCCAGGGTTCA
CAGTGCTGAACTGATGTAATTTTCAGAGACCTGTTTGATCTTACCTTACA
ACAGAGCGCACCAGGTCATAGACCTTCTCCAGCGGAGTGGTTGTTTTCAG
GGGACGTAGAAACTCTATGCCCTGGCAGGCTGCAAGGAGCTCGATGGCCA
GCACTGAAACAAGAAATTCCAAGAGGGTAGCTTATGAAAGTCTGACTTCA

FIG. 3.1

TGCTTAAGGAATGTGGATTTCCCAAAGTTGACACCCATCACCACCCAACT
AACAGATGGTTTGTTCTCTGTCTATTGGTAGAATGAAGTTGCTTTGGTAT
TTAGTTGCCATTTTAACCTGTTTTCTAACCCCTTGACTATATCTTTAATG
CTGAGAAGGGGAGAATTGAGACATTTACCTGAATAATTACCAGACCTGCA
CACCTACCCAGGAAGCTGCCCATTCATCTGCACTAGCAAAATCTGCCATG
TCCCCCATTCACATCCTCTAACAAAGGTTTGTTGGCCAAGTTTGGGTCAT
GTGGGTAGGGAAGGAAGTCAGAAAGAAGAGCTGATCCTCATCTTGagccc
cagttctattaaataattgtatgcatttcatcaagatgctttacatctcg
tggtttccaattccatatgaattgcggggtggggatactggactagaaga
tgagaaattgcttccaggtccaccgtgaattccacaacttcatCCTCTCC
CACTGTGACCTGTCTGCACTCACTAGAGTTCATAGTGTACTTcataaatt
gaatgtgctgttgaatcaaggtggggtgtgagagttcatggtactcttct
ctccactttgaatatgttttaaaagtctcattaaaaaaaaaaccactttg
ggggtgaggtgggaggatcgcttgaggccaagagtttgagaccagccaag
gcaacacagcaagaccccatctttacaaaaaatttaaaaattacccaggt
gtggtggtgcttgcctgaggtgtcagttacttaggagactaaggaaggag
gatcacttgagcctgggagttcaaggctgcagtgagctattgttgcaaca
ctgcactccagcctgggtggcagatagagatcctgcctcaaaaaaaaaaa
aaaaaaaagagaaaaaaaaAGCCAGCCAAAGGACCAGCTTAGTTCTGCAT
GGTTCCTtggttcttaatctttagtgaagatcagaatcacctggagggtt
cgttaaacacagattgctccgctctcctcctggagtgtctgaattagcca
gcctgcaaggaggcctgagagtctgccttcctaacaagtttccaggtgat
gctgatgttgctggtgggagatcccacttgagaaccacGGGCACAGTGGT
CTATCAGGCAGGCCCGCCACCCCGAACTCATCAGCATTACCTTGCTCCAC
ATGCTCGATGACCCTGAGGGCTTTCCTTGCTGCCCATCCTCCCATGGAGA
CGTGGTCCTCCGTGGCTGCGCTGGTGGAGAGGGAGTCAACAGACGAGGGA
TGGCACAGAGCCTTGTTCTCAGAAACTGCAAGAGACCAGTGCCAGTTAAG
AAGTGCTCCTCACAGGATGAGCTGTCTAAAGGACCCGTGGCTTCCACAGA
GTGCTCCACAGCATGGGATACACTCTCCAGAAGATCTTGGACATTATCCA
AGCACCTGATGGTAGAAAGCTGCTTTGGGAAAAGGAAGCAGGTCATTTTT
TTTCCCCAAGTGAGGACTCTAAAGCAATAGTGAGTTCTGAGGTAAGACGG
AGATGGGAGAACTGGGAATTCTAATATAACAAGGCCAAGATGACAACCTG
GGAAGCATATAGCATGCCAGGGAGACTAGGGGAGAAAGAGACATGATGGC
CATTTTCAGGTACTTGACGTCAATTTGGTTGTGTCACCAGAATTCCGATG
TGGCATTTGGGGACTGAGGCTGGACCCATAAATCTTGGGCAAGAAGATTT
AACACTTCAGAGTGTTCAAGGATGACATAAATGGATGTAAACAGGGGCTC
GATGACTGCCAGAAATATCTGGGAGGTGGGGGAATTCTAGGGAGGACCAA
GACATGGGACtctcaagctttccagtgcacatgaatcactcagggacctt
gttataacaaatatactgagctttgggtggggcgtgaaattctgctgttc
taacgagctctcaggtgatggccatattgttggtctgaggactacactat
aagtagcaAAAACTTAGGTTATGAAGTTCCCTCACCCTAGCTTAGAAGTC
AGGAAAGGTCAGACTCAAAGTCTCTTCTCCTCTTTCTCTGGCTTTAAGAG
TGGTCATGGGTGAGGCTTCAGTTGTTTTCTATGCTGCATGGGATCGCATC
CTAAGATGATCTCGCTTTAAACTAGGGTCATGCTACTTTGTCAAGGtcat
gttggttggccaaggactttccaggtttcagcactgtaagtcccaagtcc
ttggaCCCTAAACTGTGGACTATACAGATAAGTAAACTGTGGTAAGGCTT
GTTCGGAAAGATAACTTACAAGGGCCAAAAAAAGAAAAACACTAATTTTA
CTACAATGAAAGCAAGCCAAACAACCTCAATAGGCAGCTTGGGAAACTAA
AACATATTCAAATGAGGCTTCCCAATGTCCATCCTGTTCTCTAGAAATCA
ATGACTACTCCCCCACTACTACGTTATTGTGAGAAATTTCTACCTGTTAA
AGGGGTATTTTATTAATAAGCAAGTAAGCAAATAGAAGATACCGGTCAGA
GGAGGTGAATTCAGTGGCTCTTAGTTGGTTATTTGTGTTCGTTGGGAATA
ATATTaatagcaactagtatttttttagtgcttatgatgtgccaggcttt
atatacatcaattcatttaatcctccaaacaaccccccttaggtaaactga
tctccattttatgcaggtgtaaattgaggatcaacaggataaagaggctc
acagagctagtaaatggcagagctgggcttctgatctagCATCTACGCAT
GTAATAACTCATGCTATCCTGCCTTTTAGGGtagggttgttagataaagt
aaaggatgcccagttaaattttgatttagattaaaaaaataatttttgt
agtacaagtatgtcccaaataattcaaatttaactagtcatcctgtgttt
ttgttaaatttgacaaccctaTTTTAGGATTAAGTATTGATTAAAATGAG
ATCCTCATTAATTGAAGtaaaagcacatttttgcatgccaaaattcaggg

FIG. 3.2

tttgaattctgctttacatcttgctagctgtgcaatattgggcaagtcac
ttaactctcagatcttcagatattcatctatagataacaataatagcact
tacctcaggtgacaattgtgcaattaagtgaatgaacataaatgaggccc
ttagtacttacttagtgccaggcactgttctgaTGTGTTAATCTGTCTCT
TACAATCTTGAGTCAGAAATAAACTATATTGAAGCTCAATCTTCACAGAG
GGTATCCTGATTCTTATAAGCATTTTTTAATGTTGCAATAACATCTTTA
TGTTTTTAGTGGTTGTTATATCTAGTGAAATGAATCCAAAGTTTAATTAT
AGGTTTAAAAGTTCAAAGTTTAATTATAGGTTGGTTCAAGTTTCACCATT
AACTATAACCATCTTAGTCTTTTTCCAATAGTCTTCAAATGGAGATTTGG
AAAAAAGCTATAGAGATGAAGTTCATATGCAATGTCAAATTGCTTTCCAC
AGAGAAATTGTCCATTACAGCCTTATTATTGTATTATTATATTTCAGCAT
AACAGTATCGAAGTTTTTAAACTATTTTTTTCTGAAAAATATTAGAGTTA
ACCTGTTACCTTTGCACTGAGAGAACTAGGATGCAGATAAAAGTGGTGAA
AAGTTAGATCTCACTCACAGACCACATTTGATACTTCTAGGTGAAATGGA
AAGACCCTTAGATGGACGGGCGTGTGTTCTGGGAAAGGGGCAGTGTCCTT
ACCAAGGGCTGCTGCCGTGCAGTGAGCTATCATGAACCCAGAGTTCAGAC
CACCTTCAGCCACCAGGAAGGCAGGCAGCTCACTGAGGGAGGGATTGCAG
AGCCGCTCGATTCTTCTCTCACTGATTGCAGCAAGTTCATGGATGCCAAT
GGCCAAGTAGTCTAGGGCCTGAAAGAGGGTCTCCATTTAGTCAGCCTATA
TTGAAATGTGCCTTCTGGGTCAGGAGCAGTTTTAAAAAGCTTACTTTGGC
TGGGTATTCACCATGGAAGTTTCCTCCAGAAACTGTCTCTCCCCTATTGG
CAAAGACCATCTTTCAAAAGAGGTTAAGGCTTGAAGATAATGTTTGCTGG
TCACTTCAAGTACAACCCCTTCCTGCCTTCTTTTTAACGTGGAGGTGGC
AGTCTGTGTACAAATGTGGGGTGGAGGGAAAGAGACAAGTCTTCCTGCAA
GAGATATAAAGGGGCACAAAAGCAAAAAACAAAAAGCCTTAAAGGTGGAT
CATGTACACCCAATTTGGAGGCTGAAAAAACATGAACCTTGAAATGATGT
TTTCTCTTGAGATTAGATTCTAAAGCACCATAACTGTACTAACCTGGTGG
TTAGTACCTGCCCTCAAAAGGTTTATAGCCTGAAACTAAAAACAGAGACC
AACACATCTGTTTGAAAGCAACTTCTGTTTCTTCAATGGGCACTGCAAAT
TTGTGTTCCATAGAAGAATCTGTTGAATGGGAAACTCTGCTGATGAGCAA
CTACCAAAATGTCTGGAACAATCAATTTTGAGAAAATTTTCAAATTCTTT
ACTCAGTAATCTGGTGTCAGCGTTCAACAGCAGATGGTGGCCAATATGTC
CTCATGAATCCATTTTAAGTAGGTGGCAAGTTTAAATTTGCTGAATATTA
TTACTCTGAGGTAAttctttttttatttctgtatcattctgtcacccag
gctggagtgcaggggcgccatctcggctcactgcgacctctgcctcccgg
gttcaagtgatttcttgtgcctcagcctcctgagtagctgggattacagg
catgcaccatcacacccagttaaattttgtatttttagtagagacagggt
tttgccatgttggccaggctggtcttggactcttggcctcaagtgatcag
cccaccttggcctcccaaagtgctgggattacaggtgtgagccaccaaac
ccagccTCAGATAATTCTATTCCATCATGCACTTTACTTAAACCAGCAAG
CACCCAGGAAAAGGCAGTAACAGATCCTTCTTCCTGGTTCTAAAGAGCTA
ATCTTTGCCTCTTGGGCTCAAGAATATTCATTACCTATTAACTGAGAACT
TGCTGTGTGCAAGAAAGTTTCTAACTTTGAAAGAGTTAGAGATGTATGTG
TTACATTAACCTACTCAAGTGTGGATTACTCTGTTCTGCATGTGTAACTG
TGAGCCCATTGGGTCTAGCTCCTTGGTCTTGGCCTCTTCTCCATTCTCTG
AATCCCTATAGCAATGGAATTCTGCATCAATTTAGAACTTAGACATGTTT
TTATTGTCCTCTAGTTGTTCCAAATTTGTTTGTTGGCTATTAGATTAAAA
CAATTAGAATTTAACTCCCATAATATCCAGCATGTGTGATGGGGCTCCGT
ATCTGCAACAGAAAATTGAGACACATATTCTTTCAGGTAACAGCAGTATT
GCAAGAGAACTCCCAAATATTAGCCTATTGGAAATTTATCAATAATTAGC
AATCTTTAATTGAAAAAAATAAAAGACTTTTGGCTGAAATTCTTGCTGAG
GCAATTGGTAGCAGAAGAATTTAGTGAGGAATTAATTATCCCCTGCCCCA
TATTCAGTAATTGAATGGTAATTTCTAAAAACTATGAGATACCCTTTAAA
AGCAATGATGTAAATGTAGAATAGATACCTCTTCCCTACAGTGAAAAGAC
TGGTACGTGAGATAAGACTACATAGAGTTCATAAAAACTACTATTCCATC
TGGGGGATGGGGTGGTATTGAGGTGAATGGAGAGACCCCACAATTTCTGAG
GCTTATTTAGTGTGGGTTTGACTTCAGTGTAAAACAATGTGAGAGAACAT
AAAACACACATTCTGAAGTAAGCTTGTCAAAAAACACATACATACAAAAG
CCATCTCATGGGAAACCTTATGGAGCTATCACATAACCATCTTCTAACTC
AGCCTGTGACCTGCTTTTGGGGCTGCTTACTCAGCACTTTCTCTAGGATT
CAGAACTGAGGCAGATGTGGAATAGGAAAAATAGATTCCAAAGGCGTTTG

FIG. 3.3

ATTATCTTCAGAGGCAGTGCTATCTCCATGAAAACTGTGCCAGTGTGACT
CCTGACTGATCACCTCAACATCTGGGGAACTGAGCCATCATGGAACATTC
CAGAGAAAAACCAGATGGCTCTGAGATAAGCCACACCATTAAGAGAGGAC
CTCCATCCTTGAGAAATGGAATCAGTTTTACTATTTCTTTGAACAAACGC
AAAAGCACTAATTTGAGCAAAGTGCGCATGACAAATAAAAACTCATGATG
GGggctgggtgtagtcgctcacacctgtaatcccggcactttgggaggcc
gaggcaggtggatcacttgaggtcaggagtttgagaccagcctggccaac
acagcaaaaccctgtctctactaaaaatacaaatattagccaggcctgct
ggcacatgcctgtaattccagctactcaggaggctgaggcaggagaatcg
cttgaacccgtgaggcagaggttgcagagagccgagatggcaccactgca
ctccagcctaggagacagagtgagactccgtctaaaaataaacaaaaaaa
aaaaTGCCAAAAACCTCAGGATGAGGAAGCCATAACTCTTTAATCAATAC
TTTGGTAAGTGTTAAAAGGCTGACCTCTGCATAATGCAAACTGCTCTCAC
TCAAAGCAGAGAGGCCTGCATAAATTGTTCAGCATTTCTGCAATCACATT
TGTGACCCACGTCTTCACCCTTCCACCAACAACCTTGGCAGTGGGTTTTA
GGGCCAGTGTCTTCAGGAAACATGTCAGCCAATGCTGGAAATATCTTCTT
AAATCTTGAATAGGTCCATTTTGAAagtacagcatgttagacttggaacc
tgagagtaagttcacaggtcacctctgccacttaccagctctgacctgga
gaaagtcagttaacctctgagcctcaggtactgattcatttactctgtga
aatggagcaatggaactgagaAGCTACACAAAATGATTGTTTCAGTAGAT
CCTAAAATTACCAGCTGCAATTCTATAATTGCAGGTTAGTATACAATCAA
AAGATACAGGATTATCTGTTGCGCTGTTCAGTTCTGTGGTAATGATGTTC
TTCACAAATGCTATTGTATCATTCACCACACCATGGACCTAAAATACAAT
CAAAATAAGGTATATGACCCATTTGATTACCTGAAGAGTACCAATATTCT
TAAAAGAATATAGAAGATCTTATCTTAAAGTTATAAAGAATACAGAAGAT
CTTATTTTAAAGTTATAACCATGGAAATTATTTGAACTGAAGATAATTTT
GTTATAATTCTTTTGGGTTTTCACTGAAACAAATTAGAATAAATTCATTA
TCATATATATTCACATTAGATCAATCTATACAAAgcagcatggtgtggga
ggaagaatgccaactctagacacaggcagattcactcccaggttagtggt
aggacttgggcaagttccttaggtttatagttaaaagataggaagactta
gaaaagagacaatagcacttatggcttttgagaagtacataaaataatgc
aaacaaattcttagatgtgactcgcagagattactcaaatggtagctatt
atCCAAGGCGGTAAAGTTCATTAAGCACGAAGGCATCACATTAGAAGATG
CTCACACATAAGGCAGCTACGCTGTACAAACCCCAGAAATAGCCACAATG
CTATAAAGCAGCACCTGGCTCTGGTTTCTCCCAGAAGTCAAGGAAGTAAt
tatctgtctgtgtgatcgtgggcaagatacttaattctgtgcctcagttt
ccccattgcaaaatgggagaaagagtatcttatagttgggaagattaaat
gaattaataaatgaaagacagtgataatggtgcctgtcacatagAATCTG
CTATCGTTATTAAAATATCAGGGAAGTCTTACATCAGGACTTAATCTTCC
TGTAGATCTAATTTGGCAATTCTTACCCATAGGTGTTTTGATCTATTGCT
CAATAAGCTAGCTAGAAAAGATAACTTGCTGACTAAAGGGAAATGAGGGT
ATTTATTCTAGGGAGGACTCTCTATTACACCATAGACTGAAATTTGGCAC
AGACCAAAATATGGTTTATTGAGATGACTGGCTCTCTAACTGTCATATGT
AAATTACACATCTGTAATACAGATGCCTAATGCCAACCCAGGTCATCTGC
ATTTTTAATTTAAAGTTAAGCATCACAAATTCATTTAAAATAATTTATAT
TGCCCATAAAATGCAAGTAAGGTATAACCATTACTATGCACCTGAGTTTC
AAAATGATATAATTAAGACTTTCCTGTAAACACCTCTGACTATCTGGTTA
AAGTTTCATCTTAACAGGGAGAAACAGTACAACTCTACTAACTGGTTATG
ATTTTATTACTAAGAATTTTTAAAAGTTAGGGCACTGAATCAACATAAGA
GGTTGTCTGggccggggacggtcctcacgcctgtaatcccagcactttgg
gaggctgaggcaggtggatcatttgaggtcaggggttcgagaccagcttg
gccaacatggtgagaccccatctctactaaaaatacaaaaattaggcatg
gtggcacatgcctgtaatcccatctactcgggaggttgaggcaggagaat
cacttgaacctgggaggtgaagattgtagtgaacagagatcatgccactg
tactccagccagggtgacagagtgagactctgtctccaaaTCAAAGAGGT
TATTTGTTGGTTGTCTGTCTCaaaaaaaaaaaaaaaaaaaaaaaGAGGTT
GTCCTCTGAAAGTAGGTTGAACAATCAAAAGAAAACAAATAGTTCACCAT
ATAGAATAGAAACTTTACAACAATTGCACACATAAAGGTAAAATATACAT
AACTTTTCATAGAGACAGTAAGAAATTTGGACTATAGTTGACCATTACAT
GTTTTTCTAACACTTTCCTATTTTAAAATTTTTCATCCTGAACCTGGGGA
AAGAAAAACTTTATTGGCATTTTTTATTGACCTTTTTTTTTTTCTTTATT

FIG. 3.4

TTACCTGTGGACAGCAGCGCAAGGTGTATGCATCCTGGACGCGATCACAG
AACCTGTGACTCTCTGTGGAAGAGGTGGAGGGGATGAGACAGGGATCATG
TTACCAATTCTTTTCACAAAACACGTAACCAAATAGGTCACTCCCATAAA
CATGGTCAGACCTGCTATTTCTGATGGGTGGTGATCTGAGTCCAAGAGTG
ACCGAAACCGAAAAGCAACTTCAATTTGCCCACGGTGAGGTCGAAGAGCA
TGAATGTCTAGAATTGATGAAGGAGAAAAAGTCTGAATAATTCCAtttat
ttatttttttaaagatgggggtctcactacgttccccaggctggtttca
aactcctgggctctagcgatcctcctaccttggcctcccaaagtgctggg
attacaggcatgagccaccatgccaggtcGAGTAATTCTGATATTAGAAC
AAATGACCATCAATGGTTCAGGACCATCTACGGTGCTGACACAGCCCTCA
AAAGTCCCAGGGGTCCTTAGCCACCACTCAGAATTAGAAACTTAACTCCG
AAAGCACGATTTTCCTTATTGACTTGACTCCTTCTACTTTAAATATCTGA
GAGCAAACTATATGTTGAGACCACTGGGAATTCCACTCAAGACACTGGGC
CTACCTTAAAGGAACAGGGCGAATAACAGGAGGGAGCCCTACAGTGGCCT
AATTTAACTCATTCACTTTTAGACAATGTTCTGCCCTTTTTCATATTATA
GTTGGGAGGTCGTCAAAATTCACTACTTTCTAAATAAGCTACCAATTCGA
CAGTTTTTCTTCCCCAATTTTCTAGTCGGGACCAACTCTAATCCTACTCC
TTTTTACAGGACTCCTAAGTCCTGTAAAAAGATTCCTAAGACAGCACAGA
GCTTGACACACCCAGATCCctgggtgctctcaggcaagtcactcaacttc
cgggctgtgtgtatctgtaaattgCAGTTCTTTCAAAGATCAGTTGTGCC
ATAGCCTAGATGAAGAGGCAGCACACTGGGTACGCCACAGGCACTTGGGT
TTTCTCCTTCCCTACTACCTGCCCCCACCACTTCTGTGTCTAAAGATCTC
AGCCACCCCGCCCCACCACCTCTGGTTGAATGAATAACAACCAAAAGGAA
GAACCCTGCTGACCAGTGTCAAAGGCTTTGGTGGTGCCCTTCAGCACCTC
AAGGGTCAGGGCTGCCACAATGTCAGCCTGCCGTGCAATAGCACTGGCTC
GCTCTACAGCTTCACAGCCCAGGGATGTGATCATCTGCGTCCCATTGATG
AGTGCCAGGCCCTGTCGGGGGAGAGAGCAAAGTTTCCTACTGTGATTATT
GTAACGAACCTACATACCCGTGGATTTTGTATCTTTTGCTTTCATAAGAG
AAAAATTAGCCAGTCATAAACATAAAAAATTATGTTTATGTTTTCTAAAG
TGCGGGACAGTAATGTTTATTTAAGCCCTTGAAGAATAAGTGCTATCATA
TGTGAACTCGTAAGCACAAATCTGGCAAATGAAACACTCATTAAGTATCC
ACATTCCCAAAGCAGCAATGCAGCTCTGGAGTGTAGACTGCACATAAAAT
CTTTAGTGCATTAGGTTGCATTTCTTCCTTAAATTCTTACTGTTATAGAT
GAGACATCCAAAAAAACCCAATTCTGGTCCAAGACTCTTAGCTTAGAGCA
TTCTAAGGAATTTGGGCTGAGAACATCTATCTCTCAGAGATCCTAACAGA
ACTCGATTTGAAGTTTTAAGTTCCTAAGAGACCCCCTATGCATTGTGGCA
TGAAGAATCttttttttctttttttgagacagggtcttactgtgttgctcag
gctggtgtgcagtggtgcgatcatggctccctgcagccttgacctccagg
gctcaagtgatcctcccaccttagcctccagggtagctgggattacaagt
gtgcgccaccatgcctggctaattttgtctttttggcggggcgggggg
ggcgggtagagatgggtttcaccatgttgcccaggctggtctcaaactcc
tgagctcaggcaatccacctgtctcggcttcccaaagtgctaggattaca
ggcatccgccaccatgcctggcATAAAGAATCTTTTAAATTCTTACGGAG
TTGCCCCTTCTTCAGGGATGAACTTTAAGCAAACATGCAAGTTGCATTTA
AGGAATGATTGAGGCTGAGATTAAAACTGAAAATACTGCATAAATAAAAA
CTCATGCACTATGAACATATTTTTCTTGAGTTTCCTTACCTCTTTTGGTT
TTAAAATAACTGGTTTCAATCCATGGGCTTCTAGCACCTATAGAATGATT
AAAAATATGAAAATGGGTATCAAATGAAATACTAGCCTATTTCCAATATC
ATATGGAATCCAATAATAGCTCTTTATGCCCAAAAGTCCATCTTATAAGA
AATGAGACCTACAGGAACTGGCTGTATTCATGTTCTCTGGTCTATTCTCT
AGTTCTGTTCTTTAGTCATGAAAGCAGACTTATCTTTCAATTAATTTTTG
TACTGAAATCAGGGGCTCCATTGTCTATAGAATCAACCCTAAATTTTGGT
TTCTACGTCCTTCGTGTTCAGTTTCTACCTTAGCAGTTCACCTTTTTTAC
CACTGCCTCCTGACATGCAGGCATCTGACACACATACATGCATCTGTGTT
GTGCTCAGGCTGGACTCCTCCCAGTTCACGCTCCCTTGCCTCCAGAGCTT
GACCTAAAAAGTCCTCTAACCTCATTAGTGCTTCATTTAAATACTGGCAA
AACCTCAGAGCAGGGTTTTTGTGGCACATGTGTGAGCACCAATGAAGAGG
GGATTATAAAATTCCCTCTACTAGATGGAGACAGAATCCCGAGGGGGGCGA
TGGGCAGAACAATCTTCCCTTGAAAGAAAAGAAGTAGAGAGTCATTAAGT
TAAGGTCTCTCTAGGAAAGAAGGAAGGGGAAGTTAAGGTAAGAGAAGGAC
AGAGCTGGTCCCATTTACTACGTCAATTTCACAGATTCAAGTATCAGCTA

FIG. 3.5

GAGGCTGGATTCTGTTCTGGGTGTTGGGGTCGGTCTAGGAGTAGGCAAAA
TGAAGACAGGCAAGCTCAGGGCAATCTGAGTAATAGTACATTCAGTGCTT
GAGGATGTGGGAAGTGGGTGGGGTGCAGTGGAAAACAATCATTTGCTAGG
AGAGCATACAGGAGGGTCACAAGGAACTCGAGAGGTAGGAAGTGGAGCAG
CGGAGACGGAAGCTTCTTAGAGGGCttttctatttttctttttattttt
agacacctgtctctgtaacccaggctagagcgagcacagtggtgcaatcc
tagctcactgcagccttgaactcctgggctcaagtgatcctcagcctcct
gagtagctgggactacaggcacatgctactgtgccaggataatttttaa
ttattttatgtagaggcggagcctcgctttcttgcccaggctggtcttga
acttctggcttcaaaagatccCTAGAAGATGTTTCAGAAGCAGAAATAGG
AGAGAGAAGAACGTATTTGTACCAGACCCTCTGCCCAGAACATTCCTTCT
CCAAGCAACCTCCAGTTTCTGCAATGCAGAACCACACATAGAAGGGATTA
GGGGCTAATGTGACAAACAagacccttgaaagccactttaagtttagcct
ttatcctgaggacaatgggaagcattacaagttttcaccagaacatgctt
gaatttgctgtttagaaaggtcagggtgattgctgtatgagggtggtcgg
aggaaaacGCTGTCCATAGTGAAATAATCAAAGACAAGCCTGCACGGAAG
ACAGATGATCTAGAAGCTGCATCCCCAAAAGGATTATCTATTTCCTTAGC
TGTTTCCTCTTCTGGGGCCCTCTACCCCTTTCACTTACTATCAGGGAAGC
TCCCAGCAGTTCATCAGGGATGATACATTAAATGATGCTTTATGCTGCTG
TAATGAAATTCAGACACAGATGAAGAAAACACCAAAGCTTTATCAAAAAC
AGGCTTTTTTGATTAGCCACTAGGGTAAGAGCTTAGGGAAAAAATGAAACC
TGCTTTCCAGAAGCCATATAGTAAGTGCTATGAGCCATACCACTGCACCT
GTGAGACCAGCTCGTAATTAAAATTGTGAGAGTGTGTGACCTCCCTGCTA
GGCACTGGAAATGTTGTAGGTGCAGGATAAATAGTTGGGATTAACAGTAG
CAGTTATGCCTTTTCACCAAGGTGATGACCAAACCCAGAAGGCTGACAGC
CGAGTATAGAAGCTAACAACAGTCTTGCCTAGTCTGACTtctaagctttc
gctgtctcatctgtaaagtaaggatagtaggagctccctcactgggctgt
tgtaaggactaggtgatacgaagcatgcaagcacagtTGGTGTCCAACCT
GGGGCAATTGCTGCAGATAGAAGCTGCTACGAGTCTTACGTATTTAGCAT
CAGCCCAGCCACTCTTCGGAGACCACATCTTCCCTTCTCCAACTAGCCCA
AGAGCAAGATGAGAGAGTGGGGCAAGGTCTCCACTGGCACCAACGGTTCC
TTTCTCTGGGACATAGGGCAGGCAGGAGGCTGGGAGAGAAGTAGGCAGCA
ATTAGTTCAAGAGTACTGCATTCTGACTCTCCTTGCTTTGCCAGTGAGTG
CCCCCACTGCCCCCGCAAACACCCTGCCTCCAATATCTATCACTTTATGG
CATAGATACCTGGGGAAAGACAATTCTTCAAACCCAGCTAATATGTAAGG
GACCTGGATGAATTGTTATagaaagaaaaagaggagtgggggtggagagg
aagaagagagaaaggtaaagaggagacagggaggaaaggagggctggagg
gaaagtcagcaagaaggaaagaagggccaggcgcagtggctcaagcctgt
aatcccagcactttgggaggccgaggcgggcatatcacttgagcccagga
gttcaagaccagcctgggcaacacggtgaaaccctgtctctgcaaaacat
acaaaaattagccaagtatggtggtgcatgcctgtagtcccaactactgg
gaaggctgagatgggagaatcacttgaacccgtgaggtggaggttgcagt
gagccgagattgtgccactgcactccagcctgggtgacaaagcaggatcc
tgtctcctaaataaataagaagaaGGAAGGAGGACACTTCTGGATGCAAA
GCCCTCAAAATCTGTGTGCTCTAATTCAACCTAGTACTTCCACTTGTAGA
AATTTTAGCAATATATCTTGAAGAAGTGATCAGGAACTAGCTGttttttt
ttgtttttgtttttgttttACAGTTCATTGTTTATTATAGGAAAAATAGT
TAGAAATTATCTAAATATGAAATTAAAGGACATTCATTTGACCAAGTTTA
GCCATTCACAGCTATTGGAAAATGTTTGGAAACATTGGAAAAGTAATATA
AAATGTTCCAGAAGGAGGTGGTGCACCAAAGCATTAACAAGGTTTCCCAG
GGGAAGAGAAGTCATAGGCAACTGAGTCTTTTCATTTTGCCAGTCACCCA
GTCTACACTCCACTGCCCCTTATCAATGAACACGTGCCATTTTCTAAGAA
ATTCCCAAAAAGTTACCAAAAAAGAGGCTTCATTTTTCTGAAATAAAATC
AGATTCCTGACAGCAGCATTTTTTCCAACTGTTAAATAATGTCAGTCGGG
TATGGCAGTGCCATCCACAGACCAACTTCTGGCTGATAGTTCACGCTGGG
GAATTCTCAGAGGTGCCTTAGACTCCCCCATAAAGTACAGGTGGGTTTAA
GGTTGGAGTGCTACTATCTGGGATTTTAGGGCTATATAGTATGGCAGACC
AAGGTAGGAGTAAAAATAGGTGTTGGAATCACTACTAGTCTGTTCAGCAC
AGCCCTGTATATACAATAGACTGCTCATTGAAATTGCTCTCCACTCATTG
GCAGATCCTATTCACGTGCCACTTGCGTCCATAACATGGAAACTCAAGAA
TGTGTTTTGCTGTTTGTGACTGCCTCAGCACTGCTTCTCCTCCCTCTCCT

FIG. 3.6

TCCCCTCAAAGAGTTCTGAGTCTCCACTGACCTAGAAGGCTTGTCCTTAC
CTGTGAGAAGGGACAATACCTCCAATCACTGCAAATCTGGTTTCCACATT
AGAATTTTCCTATCCAAGAAGAAAGCTCCAGAGTTGAGTTCCCTCATATC
CTGCCACTACATGGCTTCTTGATTACAAGGGAGTCATTAACCTCTTTGCA
TTTCTGTTCTACCCTTGCAAGAAGTTGGattttagtgtgcaagtctggcc
atcacctgggggacattacgatttcagattcccaggcaccaaccagaact
actgaattggcctttgggatggacattgatatcatgcaatttttctaacC
ATATTCATGTACCACTTAATCCAAGTTTCTTCTAGGCAGGCTTGAATGTA
AGGGCAGACTTAAGAGTCCTGTTCTAGTCTTGAAGATGACAAATGCTAGG
GAAAGGGTCTTGCAGAATAAGTTAAAGTTCATAGGAGTAAGCATCTCTGA
TCGACTTTCTCCTCTTCCCCCATCTAACTATCCTACTTTTTGCCAACGGC
ATTTCCCACTCATTTCAATTATTTCATGTCTTCTCAGGTGATTCCTCAGC
ATCTGGCCAATCAATTCTACCCTGTGGTACATGTCCAGCCTCCACAGAGG
TTCCGTCTAGGGAGCCATTGCATTACCATTAAACATTTCTATGACTTGTT
TGAGGGTCTCCAGGGAAATGCCACTGTATCCTTTGGCTAAGACATTGATC
CTTAAAGCCAAGAGCATCCGACACCTCTCAGGACTTAGTGGTTTCCCAAC
ACCTGCAAAACAGAATTGATGTTTTCTCCAAGAAAAGCAAACTCCTTTTT
GTCTCCTGACAATTGCCCTCCCTCCCTCCAATCTTTCCCATATGTAGCCC
AGCCTGCTATTACCTTCTCCTCTCGGCTCAGGTAGTTGGACTACTCTCCC
TCCTGCCTGTCTGACTTGTCTGAGCCCCATCTTCCTGACAAAGGTTAAGA
CCCCAGTTTTGCCTTCTCAATTCCCCTTTTTGGGAAGCTTCAGTGAACCC
CTGACCTCCCACTCACCTTTAGAATAGCATCCAGAGTCCTTAGCACAACT
TCTTTACCATCTGATGGGTGCTGATTGGTGACAGTCTTTCCCATCTCACT
ATGCCCATCCTAACTCATTCTTTGAGTTCCAGGCTTTATTTCCTTCCCTG
AATGCAACAGTGTCTCCATGGCATGGGACATGTGTTCTCATACCAACCCC
ATCCCTCCACCTGGCCCATTTCTTTTTCTGAGGCTCAGCTGATTCTTTCT
GCATCCCTTCTCACCTCGGCACCTAGTTCTTGAAATGCTGTTTTGAGAAA
CTAGCTTTTTGTGACTATAACTGGATAACTCACACTGTGCTGTGCTTTAT
TCATCTAATCACACAAGATCCAGGAGGCACCCAACGTTTTGACTTACCTG
AAGAATGTGAGCGTACTAAGTTGACCTGAAGCTCCCTGCAACAGAAAGGT
AAAAACCCTCTTAGATACATTGCAGTGAGAAAATGTTCCCTCAGCTGGGA
AAATGAAGGGAATCATGGTCAAATCCTTGGAGGGACAGAAGGAAGGCAAT
GGGAGAAACCAGCCAGCCTGGGTTTTCAATACCAACTCACATGCAAGGTA
ACCCAAGCCTCATCCTCTGATCTGTAAATTGGGGCAAATGTGAATTATTT
CCCTTGTTGAAAAATATTTAAAAGATGAGGGTAGGTGGAACGTGAACATA
TGTGTGTTTTAAACTTACTGTAGCTTATTGATAGGAATTACAGTTCTGGC
AAATTTCCCAAAACCTGTAGTAATACCGTAAACAACTAGAATAAAAAGAG
ACATTATGCAATTAAATGCAGGGATTTTTGTTTGTTTATAAAAAATATTTA
TAACATAAAGATAAAAAGATACCTGTTTTCTCTTTTATGATGCTATCTAT
GACCTCCCTGGATTTCTGCACCCTCTTCTCAGCTGTTGGGGTGAGCTAGG
AAAATGTTGATCAGAACTGAGCACGTTAAAGACTTCCACGGGCAACAAAA
ATGGCCAGAGGACATCTTTCCCCTCCCTCCCCATACCTTTATTTTGTAGC
GTCCCTTTCCCAAGTTGACCAGATCCTCCGTGGTCAGACGGTCTCCATCT
AACTCGATGTACTACACAAAAGAAGGGGATCTCAGTGAGTCTGAACAGCT
TGATTATTCTAACCAGAGTAGGGACACCTCCAACAGAACCAAACTGACAT
TTCAGAGATCTGATCATTGCGTGAAACATGAATATGCTAAATAAAAATGC
ATCTTGCATAAGAGGAGGCTTATTGGTGCAAAAGCATAATGCCTTTCCAA
GCCCCCTTTCCCCACTACAGAGCTGGATAAAGCCCTGTGGTTGGTTGGtt
tgtttgttttgaggcagagtctccagcccaggctggagtgcagtggtaca
aacatggctcactgcaacctctgcctcctgggttcaagcaattctcgtgc
ctcaggctcctgagtagctggtattacaggtgcacgccaccatacctggc
taatttttgtacttttagtagagatggggtttcaccatgttggccaggct
ggtttcaaactgatgacctcaagtgaactgcccacctcggccacccaaag
tgctgggactacagacatgagtcactgctcccggccAGCCCTGTTCTAAT
TGACAGTGTTTTCTCAGAAGTTTTCCTGGCTTTCCTCCCTCTTAAATAAG
GGGCCTTAATTTTCTGAAGAAAAAGAAAGTGGTTTGAAGCTTACCTTTTC
AGGCTCCCGGTACTTGCTGTATCTGTATCCAGGTAAAGGAACATATAGGG
TGGTGTGGAAAAACCCCCAGCCCCACCATCTGCAGGAGCCACCCCCAGAG
CAGACCAAAGAGCCTGTGGGAAAGGATACAGATAAACTCCTTCTGGTTGA
GATGGAATGAAGTCAGGAGACATGGCATCACCCTCTATAACTAAAACAAT
GCACGGGAGACTCGTTACAGATCACATTGTACAGCCATGTTCCCCCTGTT

FIG. 3.7

AAACCAAGGAACGGCCCATCATTGGCCCATGAATTCTATAGAAATGGCTG
CTTTAAAACTGCTTCAGATGGTTTCATGTGGTCTTAGCATCTTTATGTAG
GAGGAGAGCAAAAAGCAGAAAGGTAGGTGTCAGGGCAGAGACCAGGGGTT
TAGATGAAAGTTCAAGACAGAATTCCACTTCCATCCCCATTCCCAGCTTT
ATTTTCTTCAAAATCTGAACTGATGCTATGCTGCCGGCCTCCAGTCTGGG
GGTGGGGGTGGATTCTTTCGAAAGGCAAAATAACCTCAAAATGATTCAGT
CACTGCAAAGggattcagacctgcagccttgagtaccagtctagtctttg
ttacttactagctgctggagtctgggtaagttacctcctctctgatttct
cctccatcagaggtggaggagaatcctacccatctcacagggttgtgtga
ggacttaagatccccagaggcgtggcatgtgcctgcacagggccagcctc
ggcaagcCTGACCTCTGCTCATCATTTTCCCTGAGGTGGGGTTCAATGC
TGCAAAGACTAAGCCAGGCCAAACCGCACCCGTTCGCGGCCCTCTCCTGC
AGCCACTCACCCACTTCCACGAACTCGTTGTTCTCTAGGGCCACCTCGAG
CCGGTCCTCGTTGTCCAGCAGGCCCAGGCCCTTGCACCGGCGCACAAGGA
AGTGCGCGTCATCCACGGAGGTGAAGCCACCATTGTCGGGCTTATTCTTG
ATATAGCGCCTCACGGCCTCCCGGCCCAGCCAGCCCACAGTGAGCTGCGC
GTCCTGGCAGGGCACTGCCAGCCATTCCCCACGTACGTGCACCGTGTATC
TGGGCATGGCTCCGCTGCAGCCTGAGGTCCTCAGCTGGTCACAGGAGGGG
AGAGCTTTATGCAGGAGTGGCTACCGGGGTGTGGTCAGCTGGAAGGATGA
GAATAGACTTTCAAACCACTCCCCCTCCTTCACCTTTACTCattcatgca
ttggacaaatatttattgaggtacctgctgtCCCTTTGGTTTTTGTAGCC
GAGCAGGGGCAGGAGCAGGGGATGCAGACGGGTGAGCCTCCTGTCCACTT
TCCATCCAGACCTGCTGCCAGAAAGGCCTGGGGTCTCCCACCCTGGGAGG
TGCTGTTCTTGTCCCTGATGGCACCTACCTGCTGCTGGCCCCCTTTCTTC
AGGGTCCCCAATTTCTCTCTCTTCCCTCGTTTCTGTCTGTGTTCTCTGCC
ATTAAGGGCAGCTTATAAACACCATGTTCCTGTCTTTATCTGAGATTACT
CAACTGTAAAACGTGTTCTGTGGGCCAACTGTGACACTGGGAGTGTGGCA
ATCGTCACTCatttgtttattccacaaacatgtattgagcaactacttcc
tgtcaCCAGTAAGGTTTTCTGAAGCTTTCTTTCCACCAGGGAAGACTGCA
AAGGCCAGAGATCATTTTCACAACTAAAGGTCGTCATCTGGGCAAATGAA
CCACTCTGACTTGgagattaggggctcagacagccgtggatgagagtcca
gctctactacttattagcCTTGATTAGGTGAGTATTACCCTGTATTTCCT
TATCAGAAGGCCTAGGGGCTAACTGCCTCCTTCCAGTATGTGCAGGATTt
acctgtgatcaaatcctggctctgccatttgctaagtgtatgacttgtgg
gcaagtgatttgacttctctgggcctcagttgcctcatctgtaaaatgaa
gataatggtaatgatgatagtatatatgtcaaagggctattgggaggatg
aagtcagttcatatatgtaaagccctcaacacaacacctggcatagtgga
aatattatagaagtgtctgtgattactAGTATCTGGACACCAATACTCCA
TGTAACTATAATGCTTTATAAATGTTCTGTATGAATCATAAAGCTATAAA
GTTCCATAAATGCTCTTTCATCTTGGCACATGGATATCCCTCACCCAATT
AAGCTTCTTCACCACAGATAACTGCTCCCTGCACCCGCCTTATTACCATT
GGTATTAAGGAACTCTGGATAGCATGATTACGGCATCAAAGATATGCAGA
TGCTATTTTGACTAAGCAGCACTTTCATCGTAAGCCAATTTTTAGAGATT
TGATTATTGCACTAGAAAAATCCTGAAAAGTCTGTTTCCACTAAATCAGA
CTTCTGTTGGGAAGAGAGACATGGTTGCTCAAGAAAAACACCTATACTCA
TACCCAGAGTCCCTCTCATCTGCTGACAGCTTCCCAGGAAGCGTACAAAT
AGCTACCCTTCCTTGAGCCTTATTGAAACTTGCTCTTCAGATACCCACAC
CATGACTGCACCCTGGAATTTGTCATGACCTGAATTTGACACACTTAAGA
AATCACCCTGGAATCTGTCACGACCTGAATTTGACACACTTAAGAAATCT
GAAATTCCAATATTCCACCTTCTGACCACAACCTTCCAGCTGCCCTTTTA
CTCTAGTCACTGCCAGCCTTGGACCTGACCTCCAGTCAGTCTCTTCATCC
CTCCACTTCCCACCAGCATCCTCACTTACTATCCTAGGAAGCTGGTCCCT
AGTCGCTCACTGGACCACTCTTTCTTAAGCACTCTGAGATTCCTTTGCAT
CCCTAAACTTATGTCTACACTTGGAATAACACCCATCCCCTTAGTCATCA
CAAAAAACAGCCATCTCTTGgaaggattgcttaagcctaggcagtcaatg
ctgcaatgagttatgattataccactgtactccagcctgggtgagagcaa
gaccctgtttaaaattaaaagaaaCTGTCATATCTGTTCACCCAGGCAGA
AGACACTGATAGAGAAAGTCCTGTGATCACATAGTTTGATGGTATTGCCC
TTTTATTCCATCCAGCCCACAGTGACTTTCCAAAACTTTGACCCCTCTGC
CAGGACCTTCTCGACATCCACCTCTAATTCTCAGAAGGAGACCTTACTTC
CTACATCTGTGAGAAAACTGAGGACTGCACATGTGAACCACCTTAACCTT

FIG. 3.8

CTGCCCCACCCCCCCCCATTCATTCCttgactcatttaacaaatatttt
tcaacacctgttatgtaacaagctctatgcgaggtgctggggatgaaata
aataacaaacacgctctacattcatgaggcttactgtctggtgatggata
aagCTGTATAAAGATGACTAAtaagaggtctaactatcttcatgctgcaa
aacaacccaaactactgcatgctccagttgactgtcactgccgagaccag
cttctgagtaatttcagcccaggcatcagactagtgagggaaggagcttc
caggtgataccacctcccagccatgtaagtcacccccagcagtttgagga
ttctaaactcaggccctacgcattgtggagcagagTCTTCCTtgttattc
tttctccagaaacgcactttccaacttcctttgcctgtctagatctttct
tactccttaagcctgtttaggccttttcttctccaggaagcattccctaa
attcttcagttgggttaagtggcccttctctgggATGCCTTAGCATAGCT
CTTCTTTAGTATTATCTAGGAAATTACTTGTCTGTGTTCATCCATAATTA
TGTATATATCCGATCTGGCACAAAGACATTTAGCATATGCTTACTAGCTG
AACTGAAGAAATGTGAACTGCACCGAGCTGGCCCCTAGGTAAACCAGCAA
GCAGGATTAAGTTTGTCTTTAGCGCCCTCTACCTTCTTCACAGCACCCTT
CCATGCCACCCTTCAAGCATCCCTTGTCACAATTCACTTTCAGTATCACT
AAGTGATAACTAAAAACGACATTAACTTACAGCTTGTCTTGTAAGCTCAT
AGGGCAGAAGCCTTAAAGAGCAGTATTTGGGTAAATGGATTTGCTAAAGT
CTAATCTTAGAACATGATCTTATGCCAGTGATTTGAGCTGAACTCCCTTC
TCTGTATTCTTGGCAAGGAAGGCAAGGGAGAGCAGAGCCTGGAGAAAGAA
TCACACTGCAGCATAGATAAGTGACCAAGAGGACAGAAcgaggcgggtgg
attgcttgagcccaggagttcgagaccagcctgggcaacatggccaaact
ctttctctacaaaacaaaaattagccagacatggtggtgcatgcctgtag
tctcagctactccagaggctgaggtgggaggatggcttgaacccagaggc
tgatgctgcagtgagctatggtcatgccactgcactccagcctgggcgac
agagtgagaccctgtctcaaaacaaaacaaaacaaaaACTGCTAGGGAGA
GTGAGAGCCAGGGAAAAGTCAGGATTCCGGGAATAGGCAGGAATATGTCT
CTTCCATACCTGTCCCACCTTGGGTGTTCACTCCTATTGTAACTTTAGTC
ACTGCATTAGCACTTTGAGGGGTTATTTGGTCAGGACACCGCTCCCCACC
CCCACCCCATGCCAACAATTATACTCTAAGACACCATTCCTCTTACACAA
TTTATTTGACCAGAGGTGGACCCAACCTGGGTTAGAGTCTCACCTCTGGG
AATTTGGAATTGTGATAGCCTCCCCATGTGGTCAGAGCTATTTGTAACAG
TAAAGCTGGAGAGTGGCCGGCCTGTACAACGTGGACTAGAGAGGCAGAGG
TGAGGGACAGGAGCACTGACGGTGCTGCAGTCCTGGGCATCAGACCCCTT
CTGTCCGTCCCAGGTTCTGATAATCTCCCCATACCTAGCATCCTTAAAAT
AATCTTCCTTTTCCCTTTTTGACTTCTGGTCACTTGGATTGCTGTTACTT
GCAATCAAAGAATTCTAACACAGCTATGGTTCTAATTAATTCTAACTAAT
AGAGCTAATACACTAATAATTCTACCTAGTACAGCTATGTGTGCTGAGAT
GCCCTGGGGCACTACGTTGCATTGGCAGGGGTGCTTTGTTATGTTTGTCT
TTTATTTGGTTCAAGTTATTTTGTTGTCTTTGAACAGACTGTGAGAGGGA
TGGGAAAGACTGGTGCTTGGGGTGGCCATCTGACCCCTGATGGACAGGAG
ACCAGGACAAGCCCACTGGATGAGCCGGAGGGGTCCAGGAGGAGGGAGTT
GAGAGCTCCTGCTAGGGTTGACACATTCTGGTAAGGAGTTCATCTGCTGT
CCACCAGGTAGGTGGTGTGCAAATACAACTAAGCATTCATGTTTAAGGtt
ttttttaatttttttatttttcgaggcagagtctccattgcccaggctgg
agtgcaatggcgccatctcggctcactacaacccctgcctcccagattaa
agtgcttatcctccctcagcctcctgagtagctggaattacagtcgtgcc
tccacgcccagctaattttgtatttttagtagagacggggtttcaccat
gttggccaggctggtctcaaactcctgacctcaggtgattcacccgcctt
ggcctcccaaagtgctgggattacaggcatgaaccactgcgcccggACTT
ATGTTTAAGGTTATTTAAAAAGCAAAGCAAAATCCTAACCATGTTGAATT
TTTGAATCTGCAGCAGATTCAAATTAATGAATTTAAATCATATATCAGGT
AAAATACTACCTTGACATATTTTGTGATCATACTGAGAGAAAATTAATAT
AAAGCTAATTCAAAATTTTTTAATTTGTAAATCAAAAGATTAAACCTTGT
TAAAATTTACAAAGAATATGCCACTATAAGAAGAAGTAGCTCAACTTTAT
TTCAGTAAAATCACCAACAAAACAATAAAAAGCCAAAACTAAAAAGACAG
TTTTAATTGTGAGCTGAAGTTTTATATTTCTTTACGAATTCCATTTAAAA
AAGAGAAATCTCTAAAATCATCAATACGCAGGTCTTTAATCCACTTTTAA
GTCTTTCCCCACCAGCATTGCAGTCACGGGATGCATGCTTGCTTTGTGCT
CTTGGTAGGTTCGGACAGCTTGATCATGGGATTTGTCAAAGGCAGCAAGA
TCCCTGCCAAAAAAGAAAAAAATTGAAAAGAAAGAAAGGCgagaaggagac

FIG. 3.9

agaggaggagaaagggagggagagaagaaagaaaggagggaaggggttca
gaggaaaggaaaaaggaaggagaaagagaaTAAGAACACAAGTCAATACC
CAAGATTAAATTAAAGGATGTCAGCAGGGGTGACAGCCAGCATCACCCAA
ATAAGGCACCAGTCCCAGCCAATCAGATGGGTATGGTCCTGCCACAGGGT
CCCAGAGACCTCCTTCTGTACCAGAGACTGGCCTTTATACTGGCAGATCA
GACATTTTGCAGCAAGTTACAGGGAAGGGCTAGAGTGGCTGGGACCCGTG
GCTATTTACCAAGCAGCATGGAAGGATTTTATTATTTGAACAGAGTCCTC
TCATCTCCTGGCTAAATATCAGCCCTGTATGTGAGAGTGAGCCTCAAAGC
CTTTCTTTTTAAAAACTGCttttaaaaaaaatttttttaatCAAGATTTTA
AGAGTATGAAAACACTAAAATTTATATAGAATTTCTGAAAACTTCAAATA
ATTGAGAATAAAAGTCCTGACCACAGTGAAATAATAAATACATAATAAAT
AATACACGAAATAAATAATAAATACACTAAATAAAAAGGACCTACCATAC
AAAAGGTAGGATTAGTCATTTTTAATGTAACTACTATAAACATCATAAAA
CAGAAATACTTATTTTTCCCACAAAAGGTATACTCTTAtttattttattc
atttttttttttgagacagagtctcgcactgtcacccgggctggaggag
ctggagagcaatggcgcaatctcagctcactgcaacctctgcctcccggg
ttcaagcgattctcctgcctcagcctcccaagtagctaggattacaggtg
cctaccaccacacctggctaatttttgtatttttagtacagacagggtt
tcactatgttagccaggctggtctcaaactcctgacctcgtgatctgcct
gccttggcctcccaaagtgctgggattacaggcgtgagccaccgcgcccg
gccCAAGTATACTCTTATTTAAAAACCTATTTAAAGTATACTTTACTCAA
TTCAAAGCTAGATGGGTTTTAATTAGGGAAAGCATATAAAATATACTTAA
AACTTAATTTTGTGGTCACATCAAAAAAGAGATAATGACTTATTTTGCCA
AGTTTTATGATATTATATGgccatcacttttgatggccaaaactgcaatt
acttttgcacccacctaaATACTTGTGAAGTAAATGAAAAGCAAACAAAA
GTAATCATGGATATTTATGGCATGATTTTTTTTTCCAGAATTTGGACAAA
ATTCATAAAGACCTTGACTGAGATATTCTTGTATCTTGCTGTCAAGATAC
AACTTATCCCCCTCTCACTAAGCATTCCTTTATTATGTCAAGCAACCTAC
CCTTGACCTCTATGCAACATTTGAACACAAAAGAGTTAGCTTTATCTGCT
TATTTCTCCTTACATTTAACTTCAGACTCTCTTTCTTGTCTATACCTACC
CACCAATTATCTTCTAGTTACCTTTAAAAATCTTTGTGTATATAAGGCTA
TCTTTGATTTATTTCTATTTTATCAGTATCTAACTCTATTTGATCCAAAA
TAGTAATCCATATATAATGCTTCTAAAAAGAGGAATGAAATTATTTCACA
TTTTAAATATTTATAAGTGTGAATCCCTATTCCAAAATTATACTGATAAA
CTTTAACAAATTAAAAAATATTGTCATATAGATTACGTTTAAATATTTGA
CAGTTTTCTTCCTGTTTCTTAGATGAATTCAAAGTACGGTCTGAGTGGGT
TCTTACTTGAATAAGGGCCGGGTAAACTTCATTCTTCCTTGTTCAGTTGC
CATCTTTAGCGCCAAAGGAATTGCGTCCTCCCACTTGGATTGAATGCAGA
GCCGCAGCCATCTAAAAGGAGGATTTGGGGGGAGCATGGAGTAGAAAATG
AGGAAGGGGCAGGATATGACAGGTATATCTTAATATTACTTCTGTAGTGA
TATGAATAACCCCACTATAGTTATACTGTACACCACTTTATGGTATGTCT
TGATTCTGAGACTCTCAAATCCTTATATATACAATTTAATAATTGGTGAA
GAGAAAGAAGAGGAGCTGGTTCTTGAAAAAGATCATATATTTTTAAAGGT
CTGGATCAGGTAGGTGCTCACATACCTTATAAATCCAATTTCTGAAGGAA
TTAAACTTTGGTTTAAGCCTCACATTACAAATTTGAATTAAGAAAGATCA
GGTAGGTGCTCACATACCTTATACATGCAATTTCTGAAGGAATTAAACTT
TGGTTTAAGCCTCACATTACAAATTTGAATTAAGAAAGATTAACATATAA
TAGAATAAAATATTTCTAACTATTCCCATTTCAAAGTAGATTTAGTTGGT
TGTGGAGAAAGCCTATTTACCACGGAATCCTTCATTCTAATTTTTTTTTT
TTCTTTTAAGGCAAGAGAGGTTTAGAGCAAAGTCTAACAAAAAGATTAAT
ACTACCAGATTACATATTGCAACTATTCCTTAAATACCACTATAAGTATT
TATATAGAAGCAGTCAGTTTGACAAGGAATTCTCAAGACTCAAGTATGTC
TCATACTCTGCATTCCCTTTCTCCATCTTTCAAAGGAGTTTAGTTTTCTG
CTTTCTTCCACAGAGACAAGTTAAAATGATGTACCTGAATCGTATTTCAG
AATTGTTAATGGCATTGAAGTTGTACACCTCTTGCATTCGCTTTATGTGC
CCCAATGGAAGAGGTGCCTAAGAGCAAAATAAAGAAGTATACCGTATCAT
TTCAACAGGATTCCTTGGAAGAAAGGAGCTGGAGAGAAATGCATAGCCAG
ATTAAAATCCTAAATATTTTATAATATAGAAATAAGTCAGATAAAAATAA
AAGAAACAAATTGCACACTAAGTAAATTCTGTGCAAACTTATTCCAGATG
AGGATATTCTACTGGGAGCACAGGGATAATTTACTTTGTGAAGTATTCAG
CATTAAATGAGAATTGCTCTTCTTAGACTTTTTAGCATGTATAAATATTA

FIG. 3.10

TCTTTCAGACTTTTCCTAGAGTTTTTCTAGTTATTCTCTATAACTTATAT
ATCTTAAATGCAATTCCATTCTCCAGATGAAATCATAGTTCCTTAATTTT
TGCCTGATTCCCCCTAGCTTTATCTTTGTATATTTCCTCTGAAATCCCTG
TTAAATTATCTGCATACCTACATAATAGCAGTTCTTAAATGTTTGTATTA
TAGATCTCTTTGGGAATCTGATGAATAATGTGGACTCTTTCCCTAGGGGG
AAAATACACTTACTACATGAATACAAACTTCTGTATACAATTTCAGGGGG
TTTATAAGCATCCTATCCCTACCTTAACTCACCCTAAAAGGGAGGACAAG
TTTGGGTGAAGGAAAGAAAAAAGATGAGTTCAGTTTGGACAAGCAGAGAG
TTTGTAGTGCCTGTGAGAGGCAGAGGTGCCTCTAGGTAGATGATAACTCT
CCCCTCCAACCACGACCTCCTTACCTTACAGGACTCCACACTCACTAACC
AATCTCTGCTTTCATGAACTACTAATCCTGTCGCTAATAATTTAGTCCAT
TAGCCCCTTATGGACACATGCAACTCCAAGTCTACCCTGGTAGACCAACT
GGTTAAGGTCATCTCCAAGGCTCCCTGACTTGCCCTAAGTTTTGCTATAC
CCATTCCAGAATCACCCTACCATGTTCTCTCTCTCTGTGGCCCTAGACCA
CCCACCAGTGGTAGAGCAATTTATGAAACCATGATGACCCGATGCACTAA
AAATAGATTCTCTCTTTGATGGGTCCTTTGTTGCGTCAAAATCCTATTCC
TAATTTTTGCATCAATTCCACAGAAAATTCCGCTCCAAATCTTCTTTCTT
CTCAAGGTCCTTAGACTGAAGACTTCCCTTTCATGGAAGTCTTTAAAATC
CAGTCATTGGTTTATCTCAAAATGCAGCAACTCCTTTCGGTTTCATCTAT
TCTTTCAATTGCCTAGATTCGAAACCTTAAAATCTGCTTGGATTCTTTAC
TGTCAACCCCTATAGCCAGTCAGTCACAGAGCTCTGTGCTTTCACCCTGT
GTAAACTCTTTCTCACGTCCTGTTCTCTCCTCTCCCCGCAACTTACTCCC
TCAAGTCCGGTACTCCTGCCAGTCTCCCAACTAGTAACTTCACCACCATG
CAACCTTCATGGCCCCAGATTAGTTTTCTACAACCCAGCATTTCATCCCG
ACTCTTCTGCTGGATTTTTAAAATCTTTTCCTACTGATCAGTGTAAGATC
TAAAATTTCTTAGCTTAGCATTGAGAGTCATCACATCTGGTCCTACCAGC
TTTTCTAGTGTTACCTTCACTGACTTCCTTACCCAGTGCTACTGTTTACT
CCAGCAATGCTGCAGACGAATTCCAGCCCTTGCTGCTCCCTCCACCTTCA
ATTTCTACCTCCCTGCTAGCCCTGGGGGTGCAAAGCAAGTCTCCTCCAAA
ATTCCCTCTCTGATGCCCCCAGTTGGAAGAGTCTTTCACTAATTAAGTTT
TTCCAAATGATACCTAAAGTATGCCTCCTTTTATTGCTAATGTTTTTAAA
AAAAtttttttatgagatggagtttcactctgttgctcaggctggagtac
aggggtgtgatctcggctcactgcaacctccgcctcccagtccaagtgat
tctcctgcctcagcctcctgagtagctgggattacaggcacctgccacca
tgcccggctaattttttatatttttagtagagacgagatttcatcatgttg
gccaggctggtctcgaactcctgacttcaagtgatctgcttgcctcggcc
tcccaaagtgctgggattacagatgtgagccaccgtgcctggctTATTGC
TAAATtttgcatgtgttccccttcctactagattatacgctatttgaaga
taaggtatatcctttcttacatattttcatatttagcacaatataaaaca
cagtaagcattcaatgctttttttaaagaaatgaatAAATTTTATAAATGA
TTTTTTCCCCATTAGTTTCCACATTAATAATCTTTTGCCAAGTTGGGTAG
AACATAAATGCTGTGCCTTTCTGTCCATTTTAATTTCTAAGATTTTGAGC
TAGTACTTACCCTCTGGAGCGTCTGTGCTAAAAACTCATTCAATTGATGA
GAAGAGAGATCCTTCAGGTCTGTGGCATTGAATGAATTTAAATCATCTTC
TTTGGCCTGAAATAAATGTTACCTAGTTATTTTTGTTCAAGTACAATTTA
ATAATACTTATTGGTTTATCTGACATAAAAGTAAAAATTGAGAAAAAGAA
CCATATGAATGAACAAGATTATTCAAAATAAATTTAAGCCTGAGTTACTT
AAATAATCCTGAGATTGAGTTACTGTAATTTAAATAGCTGATATGACTCC
TAGAATCTATATTACTTAAGAAAAAGTAGATTATGGGTAGGAAGAGTGGA
AGAAACTGTTGACATTCATTGTACCATTCGAGGTATAGAAATTTCCAAAG
CAAAGAAACATTTCAAAATGTATGCATGTCAACTAATCTATAGACCAATT
CAAAAAGGTAAAGAATGAAATCGtatatttttaaatattacattaataaa
ttGGTAAGGCCATAAACTAATGTTTTCCTCCATCCCCACATATTCTGTTT
TCCCCACTTAATCTTAGAAACCATCTAAGAAAAATAAAAATGAGTCTGCA
CTTTTCAAATTTGGATTTACTCTCAAAAATCTTTGAGAAGATGATTAAGC
AATATTAAATAAAGCTTATAAAAATAAGGATTTTTAAATCTTTTAGAACT
ACTTTTATAATCTTTTAAACTAGGGCTTTTGTTACTTTAAAAGAAATATA
TGCAAATACTAAAAAATCAAATAGGACAGAAGGAAAAATTCTTTTGGATC
TGCTCCCTGTCTCCAAGTACTACTCCTCAGTAACTAATATTAGTAGTTTC
TGTATATCCTTCCACTAAATTTAATGCATAGGTATATACCCTTTTAAATA
AATATTTTGCATCTTCCCCCTCTTCAGAACTCTCTTTAATAGCAATACTT

FIG. 3.11

CTTTTCCCTTTACAACTTATCCTTAATATGAGAACTTACAGCTCCAGCTC
ATTTTCTgtgcaaaaacctgcaaatctaaactatatattaattaaggata
tatttatgtggtaaaaacataaaaagcaagagaatgataaaccaaaattc
aggacaatggtaacctggatgggtcagcaaggagggtggagaggggcata
agatggggagggatgctacagaggtaccgctaagatttacttcttatgc
tagtggtgggtcacacaattgtttTATACACCATATGAATATGTTATAAA
TATTCTTTTGCATTTATTTACTATTTAAGACAAATCATTGAGAAATAAAA
TACATAAGGAAAAGAGTGCATTAGTGAATACAGTGTCCTGAATCTGTTCC
TAACAATGCCTGTTTCTACTAATATTGAAGAGTTGATCATTATCCACCTT
AACTGCTGGGCCCAAAGGAATATTTGAGCAGAAATTAGTAGCAGTTTTAA
CTAGCACCAAATAAGCTGGAATACATTTTTCAAACTAAAACAGAGAATTT
TAATACACTCACACTGTTAAAAAATCCTGTTTCCCATAGAAATCTCTTAT
ACTTTTCTTCATGACAAGTTTGTCAACTACACAAAACAGGTTTTAAAAGG
CAATAGCTGAACTGATTGCAcagctggaggccattatcctaagtgaatta
acacaggaacagaaaaccaaatacagcatgttctcacaagtgagagctaa
acgactgtatattcatggacataaaagtggcaacaatagatactgggcac
tactaggagtggggcaagggttgaaaaactactgggtactgtgctcagta
cctgggtgatgggatcaatcataccccaaaccttagcatcacacaatatg
cacgtgtaacaaacctgcacatgtgtcccctgaacttaaaagttgaaaTT
ACGTAAAAAAATGATAAATCTGTTGCAAATTAATAGGAATAAAAGTATTC
CTAAATCTTCTGTTATTTTTCATTAAAGAATTATCAAGGGCTCATCCTTA
CTTTGGCTTCAGTAAAGGGTTCTATTTTAGTACATATATGAAGAAGCTCC
TCTTTAAGAAGCTTCATAGAAAGTGAACAAAGAGCAAAAGTGCTTCGATT
CTTTGCACCACTAATAGTCAGCAGCTGGTCACCCAAGATCATTTTAGATT
TACCTGGTATGTGAAATTGCCATATTGGAAGCAGTATCTTATAAATGATT
TAAAAGGAAAAGAAGAAAGGTAAGATGCAAATATTTTTGCATACTTTTTT
TTTTTAAGAGTTAAGAAGCAAGAAAAAATCAGGATTAATGCCTTCAACATC
AATTTTTCCCCCCATAAAACTTAATTTTCTAggctgggcacagtggctca
tgcctgatgcctgtaattccagcactttgggaggctaaggtgggaggatc
actggagaccaggagtttgagaccagcctgtacaacacagaccctgtttg
tataaaaagttttaaattagccaggcatggaggcacatgcctgtagtccc
agttactcgggaggctgaggtgggacaactgactgagcccaggaggttga
ggctgcaatgagccatgatcacgccactgtagtccagcctgggcaacaga
gcaagaccctgtctcaaaCCCTTAATTTTCTATATTGAGAGTAGATATAA
TATCACCTTAGATAAACCTGACTTTCAAATAGCCTTTCCAAATATAACTG
TTTGTGATTTAAAGTACCCTCCCTGCTTCATGAGTAAAGACATATTTGCA
CAATTCAAAAAGGAATCAAAAATCACACATTATTACTTACAGTAATCCAT
CTTTGACTTAAGGCAATACAAGCATTTGTCAGAGTCATATCATAACTGCA
AAGATAAAGATTACATTGTTTAAAAATGCACGTGCTTTTGCAGAAATGCA
GTTTTAAAGCTACAGTACATACTTAAATTTCAAAGTCCCTTTTAAATAAG
GAAAACAAACTCCAAAGTGAGGAAAATAGGAAATATTTTACCTAACTTAC
ATACTACTGGCATCATCCAAGAACTCACAAACCCAAATGGATACCACATT
AATGAAACACCCATCTATCTTTTAGAAAGAATGCCAAAGCACCTCAGCAA
AAGACTGTCATGTGCTCGAGTAGTATATGCTAAAGTAGTTGGAATCAGtt
gagcatatttagtacatggcaggaacagttctaggcactcaagacaacaa
gatgaacaacatcaagtccttgctgtcatggattttacTTGGTTGTTCCA
AACatctaatcatctaacaaacctgcaagcacctgctacataattggcac
cgttctagatgctagACCCTTGAGAGAGCCCGATACCATTGCCTGATGAT
TTCATTCCTTTTTAGAAGAAAATGAAATTAACACATGGTAATTGTTAAGC
AAATTATACCAATATTTGTGTGTTCTCAACTTAGAAATCATATTTTGCAA
CAATGGGAAAGAACATGTAGTGTGTGCAAAATTCTTGCAAAACATCCCTC
TTTCTCCGTAAATCATGCTTGCTTGTACTGAAATGCTTGTATTAGGGAAC
AGAGAGGCACCTGCCCCTTAGAGCCTAAATGAAGTAAGTTTTGATTAGAA
GTTACCACTGAATCTCCCTTAAAGAGAGTTGTGACTGGGACTCCGTTTGT
TCCCTAGGGGAGACAATAAAAAGGTCAACACAGCTCCCACCTCGAAGCAG
CTGCCAGTTTATTACATGAAGTGTCAGGCTGTGGACTGCAGGCATGCCAT
TTTGTCTTCAAGAACAGGTGGGATCAGAGGTCCTTGACTGATCAGAATAC
ACTGCTTTCAACCAAAACATTATTAGCATTGATTTCTTAAAAAATAATAG
CAAAGTAGAAAACCTTTAGCTGGTCTGTTTCTTCGTGTCCTGAAACTTCC
TTATTAGTGTAATTAAAAGTACTAAGTTAAGAATTAGCCTGGGAAAGGAC
CCTACTTATGGCAAAGTCTTCAGAAAagtaaagagcaaaaccagatatgt

FIG. 3.12

gccttgttctcatggtgctgacagtatagcgaagaggaaatactttaatc
atacgaataaataaatgtaaagttagaactgtgcaactgctacgaagaga
ggatatagcactaaaaagccctagaatgggagatttgacctggccaggga
tgtcaagaaatgcttccaagaggaagtggttcttgagctgagattggaat
taactgggcaaagggctccgggtagagaaaacagcatgctcaggtactat
gttggaggacatatggggagttcgagaaactccaaaactgccagtgtgac
tgaagcaaagggagctagagtgttaggagcttataatccccactaaagga
ttttgtcttagcccaagagcaaagagataccagtggagactgctaagcag
gaggacaacatgacacatttgtgcttttaaaggtttactctagctttagt
gtggagagtggctgggagaagtcagaacagatacaagtgcacagtttggg
tgccagaacagtcttccaggatgtgaagatgtgatactgaacttggacag
tggtagtagaaatggagagatgtggatagactcagatatTTAAATACATA
TACAAATGATGAGAGCATTATAAAAAGAGGATCGTGGAAGCCAAGATTCT
GTGCTGCAATGGATCAAAGTATTTTCTGTGGTTTGAGATTTTCTAAGATA
CTCTCTCTTTACAGAATTCCCGGGCACACGAATGATTCCAGGGTTCCTCC
AGCACTTTGGTATTACTTGAAAGCAATCTTAAGGGATCTAGAATGAACCA
ACGCCCAAAAAGGATCCCTTAGCAGCGGTGATATCAAAGAAACACTTTTG
AAGAACTAATTTTCCACCCAGATTTCCCCAATTTTAAAAGCAATGGGCAA
AGCCTTCTCCACTCCTAAACTTCCTGGAACTGTCTTTTGGCTATATCAGG
CCCCTGAAGTTAGAGTCTTTGAAAGACTCCAAACTCCAAATTCTATGCTT
TTATTCTCAGGCTCCTCATAATTCTACAGCACACCAGACTGCTGACCACT
CTCCGTACCACTTTTAAATTATTTCTTCCCACAGCTTTCTTAACAATGAA
CCTTTGAAATCTTTTTAGTTTTCCATTTATTTTGCTACCTTTCCTCTGTC
CTAGCTCTAAAATGAAGATCCTCTAAGGTTCTACAGTTTACTTCTTGTAT
TCTCCTTTGTAAGTCATCTCCAAGACGATGTCCAAATCCATCACCATTAA
AATTAATAGTTTCCTCACCCACAACACTTAATATTTTAAAAAAAATACTT
TTCATTGTATTATAATTACTTGATACATACATATTTGCTCTGTGAGTTCC
TTATTCATCATATTAGTGCCTGACAATAAATGTGTGCTGGATTGAGCTGA
ATCTTTATTACATCTCTGCTCAGTCATTTTTAATTTCTTCTTTTCTCACC
ACAGCCAATCAGTTGCCAATAGATTCTAGCCCCCAAACGTCTCTTCTCTC
AGTTACTCCTTTCTTTTCCACTGCCTTTGTATGACTTCAGGTCCTCataa
tctctagcaaggctgttgtaaaaattaacgagataatgtatggcacttCT
TAATGAAGTGCTAGGAAAAAAATCTAAAGTATTATTTTTGCTGATACCTT
TTTTAGACGTTAAAAGGGTTTACTGATGATTTGTGCCACCTGTTTCCAAC
ACAAAATTCGAAACATTCTATCGTAATCACCCCTCCCTACCTGAGCTCCT
GTTTCCCACCACAGCCTATGATAACCAGGACTGCCCAGTTAGTGGGGCGC
TCTGACCACATTTGTTCCATACTCAGAACTCCCAGTAACTTCTCAACCAA
ACACTTCTCGGCCTGGCTGTTTAAAGTGCTTTACAAACAAACATGACCAG
GCCTCATCTTGTTTCTTAGCTTCTCTCCTGCTGCTCCCTGAACATCAATT
AAACTGGCCTGTTTAGTGTAAGAGAAGCTGGTAGGCAATTTTGGTGATCC
AAAAGAAAGGCAACAAGAgaacatgccatggaacatgccatggTCAGTGT
CCTCACACAACTCGTGAAAGACCAGGGTTCAGGTCCGATTGAAGGAGGGG
GTTCAGTATAAAAAGCAGTATATTGAggccgggcacggtggctcacgcct
gtaatcccaacactctgggagacaaaggcaggtggattgtttgagctcag
gagttcgagaccagcctgggcaatatggtgaaaccctgcctctagcaaaa
gtacaaaaacagccgggtgtggtagtgcgcatctgtggtcccagctactt
gtaaggctgaggtaggaggatcacttgagcctggaaggcagagggtgcag
tgagctaagatcacatcactgcacgccaggctgagccacagagtgagacc
ctgtttctaaaaaaaaagaaggaagaaaGCAGTATAttggaggcaataag
actgccagggtttgaatctcaacttttactactcactagctgtgcaacct
agggcaagacactttacctagctaaacctaacttacctccttgggaaatg
gggataataacttataacagtgttgtaattaacataatacttataaaata
tttTTATTGCAGAAGTTTGAAGGAAGATACAATAGCTTATTGTCTAAATC
CCTCACCATCCTTGTGCAGAAAGGAGGCACTCAATTACTTGAAGTGAAAA
ACCATATTTGTAAACTGCAGAAATTATTCTTTTGGCCTCAGGGTTAAGGC
CAAAACACCTAAGAACTCTGCTTTCATCATTTACTAGTAACAGTTTCAGG
AAGGCATACTATTCTTTCAGATATTTTGAGGCTCTCTAGGAGTTAGGAGA
ATGAGAAGGAAAGCATTAGCAGGCAAGTACTTACTTGGGCTTTATGGGAG
GCAGTCCAGGAGAGTAGAGCCAGGCATTCCAATCAACTTGATTGAGAACA
TCAACCTATGAATAGTAAGAATTCACAGTTTACAATAGAATGCCCTTTCC
TGTCAAAAAAAAATTTAAACTTGTAAGTCCTTAGATATATAATTTTGTCT

FIG. 3.13

AATCTGCTATATCAAGATAATTTCTAAATCTTTTTTAAAAATTAAtattt
taaattgatagatcataattgtgtatacttatgtgacacaatgcgatgtt
ttgatatatgtactcaatgtggactaagtcaagctaatatatccattacc
tcaTCTAACTCTATCTTCTAAAATTTATATTCATCACCATACTATTGATG
ACTTCTCTGAAATAGGAAAATTCTACAGGTAGTTCATGTGGTTAAGATCA
CATTTAAAATAGAAAAAATATGCAATGAGAGGTTGAGTCCTAAAGTTCTG
AACCAATACTACTATTAGATAATACAAGTTAACCTAATCAGTCAATAAAT
AGAGATATATCGAGCATGAAAAATAGAAAAGGTTTTTAAATCCAACCTTA
TCTTTAAAATAGGAATACAGGAAATCCTTCCAGTCATCAGTAGTTATGCT
CTTATAGGAAAACTTCTCAACATAAGCTTTTAAGAATCCTAGGAAAATCT
CTAAGAGTAAAAAAGAAAAGAAATCAATTCATAGAAAGGTAATTATTTGA
CATTTTGTGTGCGTGTTTGGCATTGTACTATTAACCACAGAGAACAGAGA
ACATTCAGAGAATAGGGAAATCTACGAGGACTTTCAGAGTGAAAGAATGT
TCAAAAAAGGAGGTGGGACTTAAGTTGGGCCTTGAAGAATATATGTAATT
CAGTGGAAGGGAGAAGAGAAATTCTAATTATAGGTAAGGGGATAACACAT
GAAGACACAGAAAAGGAATGCATAACCCAAGTTCTAAAAGCAATAACCTT
CACATGACTAGAAAGGAGAAAAATAAGACTGGACAGGCAGAATGGATCCA
GGTGACAGACAGCCTTCCAAGTCAATCAACCAAGGAGAACacctcaatgt
ccatcagtgggggatgggtacataactcagcatagctttatcatgaacta
gtatgatggcattaaaaagtatgaaacagatttatatgtactgacacaga
agggtgtatgtgaaatatcgagcaaaacaaaacacaaatgcagagccaat
atatagcatgacccatttttttgtaattaaaataattacatgtatttattt
gtctgcttgttaatttacacctagaaaatgatctggagccatttacacca
aactgctaacagtggttacccctggggagtggaaAGGGGTTGATGGACTC
TCACTTGTTACTCTTATAAACTTCTGTACCATAGAAATGTTTTCAGGGAA
TACACACTATTATCCTAATTTCAAAAACTGATGAGATTTTTTAAAAAATG
AAGCAGCATAATTTAAACCTTAGGGGTTATTAATGGTTTTAAGTTGAGAG
GTAACTCAGAAAACAATACAGATTTCTTCAGCAGCTACATCCAGAATGAA
TTGGAAGTATTAAATGGAACAAAACAATAGTTTACAATTCTTCCTAATTC
TCACATTACCCTCAAAAAGAAAAAAAAAATCATAAAATACCAACTACTTA
CCTGGTCCTCCAAGCAGTTGTTCAAGGTAAAAAAGTAAAGCAAAGCCCTT
CTCATAGGGAACTGAAGAATAAGCTACATCAGGGTCTATATCTGTCAGAT
CAACCACAAGTTTGGTGAAAGGATGTGTCTCCCCAAATGTCTTTACCTGC
AAGACATGAAATAACATGGAGAAACATATAGAAAGACTGCTATCACCACG
CAAATAAGCTAATAAGGAGGTATTACTTCACTCAGTGGTGTAACTTTAGG
GGAATCTAAAACTTGGAGACTGGAACACTAGGATATGTTGGCATAAACTT
CTGGAAGTCTATTAATAGAATGCTTACTTAAGTAATATTCTCTGTTGTTT
CTTGCTCAATAATACAGGCTTTATTCTTATAAAAAGACTAGAAAAAATGAT
TTAATGCCTGGTCAGCAAATTTGGCTTTCAGGAGACAACACTTAAAAATG
ACATACCAAATAAGATGCAAACATAGTAAACAGCTATATTAATAGCAAAG
ACCCAGTGAGGTCCCACAGCTCCCTATTTAGACCAGGTCATCAAAACTAC
CTTACATAGAACAGTGAACAGTGTGGATCAACACAGTGTTATACCAGCAT
TGACTTCACTTTCCACACTTGTAAAAATGACTTTTTGGTTGCTACACAGT
AAAGACGCTTTTATAAAAACTCAGTTTTTAACACCTATACAACTTTGGAT
GAAGGTTTTTAAAACTTTGACTCCTTTACCGAATTCTGTAGTTCTCCCCA
TCCTCCCAGAGCATTAAAATGTCTGAACTTTTCACCAAACAATCGTCCGC
AAATGTGGCGTTCCAAGTACACAGTATGTCCCTCATTTAACCTGaaaaaa
aaatattttaataaaaaCACGGACACAGCTGAGAAGAAAAGACATTTCAA
TCAAGATATTTTCTTTTTGGCTTTTCTACAGAGGAAAGCAGTTGTAAGGC
ATGACCACTACAGTCTAAGCCGACTCTGGCTCCCAGGCAGTCAATCCAGA
GCAATGGGAAGCCCAGCCCAGCAGATGGCAGCAGGGAAAGTTAAGCCCTG
CTTCTGCTCTTGCATGTCCCTATGTTAAAAGTGGGAGTATATCAGGAATT
AAACTTAACACCTAGACTGAACCTAACACTCCTAACGCTGTAATAAGTGT
TACAGAATTTTTAAGAACTATCCTTGTTggccgggcatggtggcccacgc
ctgtaatcctagcactttgggaggccgaggcgggagaattatctgaggtc
aggagttcaagaccagcctggccaacatggtgaaaccccgtctctactaa
aaatacaaaaatgagctgagcatggtggcgtgcacctgtagtcccagata
ctcgggaggctaaggcacaagaattgcttgaactgagaggcagagagatc
acactactgcacaccagcctgggcgacagagtgagactccatctcaaaaa
aaaaaaaaaaaaaaaaTCCTTGTTggctgggcgtggcggcttatgccta
taatctcagcactttgggaggccgaggtgggcggatcacttgagctcagg

FIG. 3.14

agtttgagaccagtctgggcgacatggtgaaatcccatctctataaaaaa
tacaaaaattagccaggcatagtggcatgcgcctttagtctcagccactt
tggaggctgaggagggaggattgcaaccctggagttgcagttagcagaga
ttgcaccactgcactacagcctgggccacagagtgagaccttgtctccaa
ttaaaaaaaaaaaTagctgggcatggtggctcacacctgtaatcctagc
actttgggaggccaaggtgggtggattgcctgagctcaggagttcgagac
cagcctgggcaacacggtgaaaccccatctctactaaaatacaaaaaatt
agctgggcgtggtggcgcatgcctgtaatcccagctactcgggaggctga
gacagaagaatcacttgaacctgggaggcagagcttgcagtgagctagat
cgcaccactgcactctagcctgagtgacagagtgagactccatgtcaaaa
aaaaaaaaaaTCCTTGCCTACCTAAGAGATGATAACAAAGAAAAACAAGA
GATACACACAAAACAATTCAGAGTGGTAGGAGGCAGGGAAAAAAAAATCA
GCAACATGAACCAATAAAGAAATAATAACAAAAATCTTACCAAAAGTGAT
CCCAAGTTTTGTTGGTCACTAGATTCCCTGTCCAGCTATGAGATATTTCA
TGTGCAATGACCTAAAGAAAACAGTGTGATTAATAGTAAGACTGATTATC
TTAACCTAAAATAACCCATTCTACTGTAAACACTCCATGTTATTCAATTT
TTAAAAAATATTAGCTGAGATATTCAGGGAGTTACTCAGTTCAGCAAAAT
CTTTAATTTAACCAAAGACATACACACACACACAAATATGGCATAAAGTA
ATTAGAAAACAAAAATTACTTAGAAAATATTAAATAGATATATCACTGCA
TTAAAAATATTTCATAAATATATGAAGAGATCAAACCATAAAATTTCCTT
AAATCTATTACATCTAATTGTTAATAATGTGAGAAGAGTCCCCAAATTGT
CCATTATAACCATATCTTTAACATAAAAATACAAGGGATATTTTAAAATC
AGTTGACGTAATACTTCTTGAAGGTAAGGCCATAATGAAAAAGTTTAACT
TACATTGGAGAGTGACTTGTCGCCTGCCTACAAAAAAAGAAAATTACCTT
AGTATTTTAGTAATCGAATTACAGACTATCTAAAAGACTGCCTACCTAAA
TACTTAGCATACTGGCACTGGTGATCCACTGTATTTCTACTACAGCACTT
CAAAGAAGGTAAAAGAGACCTTAATTGAAAAAACAAAAAAAATACAGAAC
TAAAAATTAGCATCATTCTTTCTTGCCCTAATTCTAGGGAATTTTTGCAA
TACAATGAAAGCCAGTCTATTTGTGTCTAACTTCCATGAAACATTTCTTC
TACTTCCATTTTTATATCTGCTCTTATTTACCCATCACTTTCTTTCTCTC
CTATTACCCAAAATATATTTAATAAAACTTTAGAGTGTCCTATGTGTCCT
GTGCTGTATTTTATTTATTTTATTGCTAATCCATCACTCATTTTGGTTCT
AAGAAGAATTTAAAGTAGCTCACAGGCATATTAAACATAGCAGCGTTCTA
TGGCCCTAATCCTTTCCTGTACATGGTGTACTGATTTTTTTTTTAATTGT
ACCTACACACCAAGTGTAATTGGTATAGTCTGATTGTCTGGATACATAAT
TTATCAATGAATTGTTGTTACACAGCACCCCCATGCCCAACTCCCCAAAT
ACCGTGAACATAATATTCTCCTTCTCCAAATGGCCTGATTATTTTCCTTT
CAAAAACAAGATGGAggcctggtggggtggttcatgcctgtaatcccagc
actttgggaggccaaggcaggtggatcacgaggtcagaggatcgagacta
ccctggccaatatagtgaaaccccatctctactaaaattacaaaaattag
ctgggcatggtggtgtgcacctatagtcccagctactcaagaggctgagg
caggagaatcgcttgaacccgggggcagaggttgcagtgagctgagattg
tgccactgcactccaacctgggcaacagagcaagcctgtgtctcaaaaaa
caacaaaaaaaaaaTGAGATTGTGATAACCACAATAAACAATAAAATTAG
AAACAAAGGTTACACGAACAAGAGAAAAGATTTTTATACATATATACATT
ATTAGGACTCTAAGGTTCTTTACATATATATACATATTATTAGGACTCCT
AAGGTTCTTAAGTTTATTTTTGAAACGTCAATTTCAAATGAAGAAACATT
TACACTTACCAGTAGAGTAGGAGTTACAAAAGTAAGGCAAGGATTCTCCA
TGCCACCATAAGGGAAGGATGGTGGCAGGACCAATAGGTCATACTGTCCC
CATACATACGGTCCTCCCAGATCTTCTGCTATTTTAAGCATAGATTCAGT
CTGAAAAATCAACATATATATGTCTGTATGCCTTAATTATCACCATTGTA
CATTTCTTAAAATTGTATATTGCTTTCTATGAAGGTTACAAGTTAATGAT
TTTTATGTTAAATGAAAATGATAAAAAGAATGTAGCAACTACACATCTAC
ATAAAAGACAATCTGGTTCTTTCCCCGTATCACTTAAAACCATCACATTT
CACACTCAAAATCTTCAATCTACTGTCTATCACAATGATTACAAAGGATA
ACTAAATGACCAACCTCAGAAAACTCATAAGCAGACTTTTCCACCTGCTC
TTTCTCAGACCACACCAAAGTTCTTGGGCCAATTTGCCTGCAAGATTAAA
AAGCTTAATAAAAAAGAAATTCATGGCAAATGATTCATCTGGTTCTAAAA
AGTAGTTAATGTCTTGTAGACAAACCTTTACAGTGAGAGTGCATTTACCA
TGTGCCTATGGGAAAGGGATGAGGTTACATGGCGTGAGCTGCAAACCTGC
TGTTGTATATGCAGCAATAGATATGCAGCTCTCTAAGGAGGTACAGGCTG

FIG. 3.15

GGCCAAAGGAAAAAAACCAAGACATAAGGTGTCCCCAATTAGTTTATTGC
CTCTTGTAAGACCTCTTGAGGGTCTCATTTCATCCCTCAATTTCACAACT
ATAGAAACCCAGTCACAACTCATAAGAAACTAttttttttttttttttt
ttttttgagacggagtctcgctctgtcacccaggctggagtgcagtggca
cgatcttggctcactgcaagctccacctcccaggttcacaccattctcct
gcctcagcctccctagtagctgggactacaggtgcccgccaccacgccca
gctaatttttcttttttttgtatttttagtagagacagggtttcactgt
gttagccaggatggtctcaattccctgacctcatgatccgcctgcctcgg
ccacccaaattgctgggattacaggcgtgagccaccacgcccagcGtttt
tttttttttttttttaaatatacagggtctcattctgttgcccaggctg
agtacagaggggccatcacagctcactgcagcctccacctcctgggctca
agcaatactcccacctcagccttctgagtagctgggactacaggcataca
ctaccatgccccgattaatttttttatttttttgtagagacatgatctcact
tatgttgcccggcctggtcttgaactcctgggctcaagcgatcctcccac
tttggcctcccaaagtgacgggattacaggcatgagccacagagcccagc
cTGTAAGACTATTCTAGAACAGGAATGGGTATAAACTTTGTCATGCACTT
AAAGGTTGAATACTCTTATATAAGAAGAAACAAATAGaaaatgaaggaaa
tcctgtcagatgctataacgtggataaaccttaagggcattatgacacct
tgaatgaaataagccagacacaaagagataaaatcatactgtatgattct
acttatgtgaggtatctaaagtaatcaaattcataggaacagaaaataga
atgggtgttaccaaggactgggcggtgggggaaagaggagctattgttta
attggtgcagagtttcagttctgcaaaatgaaaaatttctgaagatctgt
ttcacaacaatgtggatatacttaacactactgaaccgcacacttaaaaa
cagttaagTGTGCTTAAAACTAAGAATGAACAAAAAATTAAGAAGGAAGG
GCACTTTATTTGTAAAATATTGATAAAATATCTTACATTTCTGtaatatt
tgtaggcttccaagttctttaatatattttatctcatttgtttcacataa
ccacccctatgaggtagaaagtcagacattataatttcaaggataaggaaa
cagagattgagagtgacttgttcaagcttacaTGAGAATCCAGATCTCTA
AAGGTAAGAGCATGCTCATTTTACAATACTTGAAAAAATAAGGGGTAACT
GGTCAAGATTTTTAAATGTAAAATTAATTTGTTGCCTACATTTTAGATTT
GAATTTTTCTAGAGCTGTCAGCTTGATATCTTGAGAAATATGCAAATGAT
TGACCAATTAACCTTGAGAGAAGTTCAAGATGCCTAAGTTTTGATCTTTC
CACAAACCTGAAAATTTTTCCAAAAGCTCACCTGCTTTCTAAAGCTCCAA
CAACTAAAGCAATCAGGTAGCAGGGTATTGGAACCTAAAGAGGGCAAACA
AACGCACACCACGTGCTTGCATTAGTGTTCACAAATGTTACACAGTAAGA
CAATTCATATTTAAAAGTAAGTAAATTCCCTTTCAAATCTCCTAATATTA
GTAGGGATAACTTTGCTTTTATACTTCTCAAATAGTTCTCATCTTTAACA
TATAGCTTAAAATTGTGATATAAAACATTGTTCAAAACATCTATTTGCCT
TTTATTCTGCTAGGAACAAAAGCTTCTCACACATGAAAAACAAGATCACA
CATACTATTAAAAGGTGCATTTTGAGCATTTCTCAAAAAGTAACCTACAG
GAAGCGCATTTCCCATATGTTTGCCTTTTTCCTCCTGACTTTTAAAAGGT
TTTGGTTTCTTTTTTTATTCCTTTATGTTTCAAAGCACTATTGGCATGT
TGTAGAGGCACACAGAGTTACCCGGCAATAAGTAGATGCCAAAGTTATGG
GAGCTTGGAACCACAGAAGCTGCAGTGGAAGTCAAATTATCCATTGTGAG
GTCAATTAAGAAAacacacacacacacacacacacacacacacacacact
cacgcatgcatacacaTTCTGTTCACTGAAGGTCAAAGATACATGTCTAA
TGACCAGGACTGTAACTGAGTGCTTTTTTGGTCTTGACTCCTCCATTTGT
AAACACTCTCAACAGCCACTTGCCCACACTGTAGTACCAGGGCAGGTGAA
TGCGTAAGAACTCAAAAGAACAGGAAGCCAGCCCCTGAACTGGAGTGAGG
GAAAATGAAAACAGGTATGCTCCCTATTCTGTCTCTACAGCAAACCCTCT
CTTCAATACAACACTCTGTAAGTAGAACAAAACCCTTTAAAAGCACAAAA
GAAAAAAAAATGAAGAAAACAAAAACCAAAAGCTGTTCTCAAAATTCTGA
AATATTTCAAAAGTAATTTTGCCCTCTGGATGTGTACAAGCTAACTGTAG
TTTACCGCCAATGAAAACAAAAATCTAGACCCTAGGATCTTACTTTTTGG
ATGAATTTGTATATTTTCCTGCTTGGGTCTTCTGGGTCAGGTGTTTCTCC
ATCACGAATAGCACTCATAAGTGCCACCAGTTCTTTAGGGACAGACACCT
AATCAAGGAGAAAAATCATTTCTAGTCATAAATAAAAGCTTCTATGTGTC
TTAAACCATATATGTAAAATAACCTTTTCTTCCCATTCTTGACTATCTAA
TAAACAGACTATGAACACAAAAAGtatatacatatacaaaaagtatatat
atacacacacatatatatgaacacaacgtgtatagatgtgtatatatatg
cacacatatatatgtgtatatatataaaacacatatacaaaaagtatata

FIG. 3.16

tatacacatatacatatCAGTTTTGTAAATAAAATTAGCAATATGGGAAA
CTGGCTTCTTTAAAAGTGAATGTGAAATTTCTATCCATTCACCCATGCAC
ATTaagagcagagttttggtagaaactggattaaaatcccagctctgcca
cctaataactaactgcacaaacttgggcaaataaatataacccccgagcc
tcagtttccccatcaagtaagtgtaaaacttcaaaggcttgctgcaagga
ataaataatataagtgaagagcccagcaccatccctggcaATGGCAGCCA
CCATCCCTGCTCCCGCTACACTCACAAAACAGATTCAAAAGGACGTTATA
TACTCACTGTAGGACAGAATGGTTTTGAACAATTTTGTTTTGAAAACACA
CACTTGGAGTTACAAATAGAGGAACATTTTAAAAGTAGTAACTGTGAAAA
ACTAAAATTTATTGCTAAAAACTGTCAAATAATTTTCTCTGGAAATCCAT
ACGGAAAAGACCCTTATGCGGCAAACCATATAGTCATTTAACTGTGTATC
CTAGCTCCATGATTCTGAAAGTTTGATTTCTGATGAATGCCAGAATAAAG
GACTCCCCCAAGTATTAATGATCAAACAAGAATATATTCCAGTAGGGGCT
AGACTTTCATGTTCTTCTTGCATGGCTCAGGACCCAAAGCTGTGACTGAG
GCAGGCACAGAATTAGAAGTTCCTGAACCAGTGCTACAACAATTGTAGAT
TCTAAAGCACAAAACTATTCAGGAAATAATTCGGTTCAGCCACCTCCCTT
CATTTAGGTGGTGATACGTTATATATATGTGCCAGCTGAGGTTGCGAGGT
CATAAAACTTGTTCAAGTGTCACATCATTAtttatttattttttagaaa
tggggtctcgctatgtcgcccaggctggccttgaacttctgagttcaagt
gatcttcccacctcagcctcccaagtagttgggacttcacgcAGTTATTA
AGTGGTGGAGAAGAGCCAGAGCCCTGGGATTCTTTGCCTCCAAGTATAAT
ATATCACTGCACTATCCTAGATGTAATTTGGTTGTGGGATGATTTGGGAA
GCAAGAAGGCCCCATAAATATGGGTTGGTCCTCATTCTATTTGCTTGGTC
TAAGTAGGTCTAGCCTCCGGGATAGTGATTATTTAGTAATTACAGTCCGC
CTTTTCCAAAAAGGATTAGCAGTACCTACCAAGGGAATAAGTTGGAATTG
CATACAGACAAGTCTGGAATATATGCCCACTAGGCTTATATGGCTACAGA
ATGCATTTATAGAAACTTAAATCATGCAAATGTCAATTTTTAAAAGTTAA
GTAAAAATTGTTCCTAAGTTCTTATTTCTAGATCCAGGATTCTGAATTTC
TTCTTTTTGTTTGtttgtttttttgtttttttgggtttttttttgagacg
gagtctggctctgtcgcccaggctggagtgcagtggtgccatctcagctc
actccaagctctgcctcctgggttcatgccattctcctgcctcagcctgc
cgagtagctgggactacaggtgcccgccaccatgcccggctaatttttg
tgttttttttagtacagatggggtttcaccatgttagccaggatggtctc
gatctcctgacctcgtgatccacccatctcggcctcccaaagtgctggga
ttacaggtgtgagccaccacacctagcccCTGAATTCCTTTTTAAAAGTCA
GATTGGTTTCCATTTCCTTTTTTTCACAGTTAAAATGTTTAAAACTGCCT
TTAAAGTAGAGATTCAGAATGAGTGCCACAGCCTCTTTGTTTACATATTT
CAGGTAGAATTTCATTAAGAAAAATAATTCTAGCTCTAGGAATTCAATTA
TCATCTCTGCTTATCATTTATACCATATTTACTGATATGCATCATTTAAT
TGAGTTAATAATTCGTAATATTTACCTCTGCAGTATAGGTTAATTTCACA
GAAGGAGTGTCCTGACAAGGAAGGATTGCTCTGCAGTGGATGGCCTGAAA
AAGGGAGAAACAAGAAGAAATAGCTATTTATCTTTCGCATAAGTCATTAA
GAAATCATTAAAAATTGCAGCATTGTTCTTAGACATTAAAATAAAAACAG
TCCTCATTTCTTGGGAtttttttttttttttgagacggagtttcactct
tgttgcccaggctggagttcaatggcatgatcttggctcactgcaacctc
cacctcccgggttcaagcaattctcctgcctcaacctcccgagtagctgg
gattacaggcatgtaccaccacgcccagctaatttgtattttgagtaga
gatggggtttctccatgttgatcaggctggtctcgaactcccaacttcag
gtgatctgcccacctcggcctcccaaagtgcagggattacaggcgtgagc
caccacgcctggccTTTTGGGATCTTTTAAAGTCCAAAAATAGATTCTTG
GACTTTTAAAAATCAGATTTTCCATTTTAATCTATGGTTAACCCTCACAT
TTCAGTTGAAGCATGGAGAAACTCTTAAGCAGTGTTTCCTACTCTATGGT
CTGGGTGACAGTAGTGCCCAGTGAGAAGCTTTTAGAAACCTGAGAAAAAA
GGGCTCTGTAGCAaaacagacctgagaagtatggcatactgcaccactgt
cttgcagagccactagaatattagccgcctgaaggctctgaacagaccta
caataaagaaacctgtttgatttCTTACATTTATGTTAACACAAAACCCA
TTTCTCTCTGGTTTAACACCTAATGGGATGTCAGTATTCTAATGAACACA
GCCTGAGAAATGTTGCTGTAATCCTGACACTTCAATCTTGCAGCAAACCT
TGTAAGTAAAACAAAGAAGCAAAGAAGGGAGAAAGAACAGTCTCTTTCAA
TACCATCTAGACATATTCATTCATATCATATGCAAAGTGTTTCTGTACTG
CCACACCAATCGTTATTAACATTGGTTCCATCCAGTATGACCACAggcca

FIG. 3.17

ggtgccgtggctcactcctgcaatcccagcactttgggaggctcagatga
gaggattgcttgagctctagaatttgagaccagcctgggcaacatagtga
gaccttacctctacacaaaaaaaattagctgggcatggtggtgcacacct
gtagtcccagctactcaggaggctgaggtaaaaggatcgcttgagcccag
gagttctaggctgcagtgacccaagttcgcaccattgcactacagcctgg
gcaacacagcaagaccctgtctccaaaaaaaaaaaaaaaGAGCACCTAC
AATCTTATACCCGGTCTGTTTACAAATAAGTCTGTCTACTGCTGGTGAAC
AATGAAATGAAAACCCAGCCTCATTGAGACAGTCTACTAAACTCAAAGGA
ATTCTGATATTAACACCCTTCTCTGAAGCTATTACAAATCCTAAACATAC
TTCATTCCACCACAAGCTTTCTTAAAACCCCCAAACTCCAGGTCTTTTCA
TTTCAGTTCTAGAAAATTCTCCAAAGATATAGGCTCCCAAATGACCTCTA
GATGGATTAAGTAGGACTAGCAGAGCCACCTGGTTCTCTCTCCCAAAATA
GATTTCCAAGACCATGCCTCTATAGTTCCTTAATGGTTTCTAGTTAGGTG
ACATGGCAACACCAAAGGGGTTTTAAATGTATTTCATTGGATAAGGCCA
AACCCAGGCAAATATGCATACAGAACAACCGTAAGCAAATTCATCAAACA
AAATCATGTCTACATGATTCCTATCACCTCAATCATTTATTAATTTAGCT
GAAATCTGTTTCCCATATTCCCACCATTGCTGCCAATAAGAAATGGAATA
ATATATTCAAAATTAACATTTTCATGACTCATAAATCTTGCATTTCTTGC
CAACTTTGGTTAATAGACATTCTATTAAGACATACTGCCTGAAAATCAGA
TATTTATGAGATACAGATTGTGCAATTTGTACACTCTTGCGTAGAACATT
TCATCTCTTCTAGATTATTAAACTGAGGGTTTCTTAGATTAAAAAGATGT
TTCAAGTGGCCATAGAAAGTAAACAGGTCTGATTCATATGCTAATTCCTT
TTTTAAATGGACTTGTATTGAAATTTGAacctaacacacaggaatattgg
gagggatgaaacatgtaaagaatctagcacaatgcctggaaatagagcaa
acgtttaatgaagtcagttcccttaATTGTAAATTATTTGATTACTATGA
AAAGTAGGTATTTTTTCTTTCAGAAGACAGTTTGAAATGTATTATCCTTG
TGACAGGTTATCTCTAATTGTATGGCTCTTTACCCTTAGTTTTAAAACAG
AAAACAAAAGTAGTTTAAGTCATGCAATTTTAAAGGTACAGTTAATATAT
TGATATAATACATACTTTTGTAAATGTGTAAGAAAAAATATGGAAAAGCTA
CATTCCAAACTCAATGGTGGTTACCTCTGGGCAATGGTGTCTGGAAAAGG
TTTGGAAATTAAATCTTTCACTTTCCATTTCTTTACTATTAGCATTTTTC
ATAACCAGTACATATTATTTATTAATTTTTCCTttcattttatgactatt
tactgagtacctactctctgctaagttctaagtcaggcctagagagtcca
atctaggtggacaTATTTCCAAACTGAAAGAAGCTTCTTATTTAAAGTAA
GGCATGAGTGTATTAATAGTGAAAGATAAAATGAAAATATATAATTCATC
TTATATGTTTCTATAAGATCAATTAATACATTTTATTAGGTAAAACCTAC
ATAATCCATAAAACCACTGTTCATTTTGCTTCATTCAACCATAGGTGCTG
AAATTTTCTGCATCAGAAATCATTCTGGAATCCTTTTTACCTGGCACTGA
CTAAAGAGATATGGGTGTTCCTTCCCAGAAGTCTGTTCAGGAGTGAGCCA
CTGGAGAGCAGAAGATTTTGGAGAGGTCTCAAAAGAAATTTCTATAACAA
TTTCTTGATTTCTGTATGAAACACATAAATATATTAGTAGAGTATGATTC
CATCTAGTGAAAATTTAAACTCATAATACATACACTGAATAATATAAATA
ACATAGTATGCATTCTCATCACTGATTGGCAGTAAGCTCTAGGTATGCCA
CATCCTCAGTGGGTAAGTCTCCTCTCAGTTTCCTACCTAATTGCCAGCC
TGTGGGTCCTTTTACCTCTCCCATGCTAACTGCTAGCGAAGGCTTAATGG
CAACTAACAGTGGTTGACTACCCCGTTGTGTGTCACGTACTTTGCATCTG
TGATATCATTTAATATTTTATTAGAGTGAAAAAGTAAAAGAAATCATTTT
TGGGGCTTCAACTACCACAGCAGCAGGTGCCACAGCATGAcacagagcag
tgctagtctgcaaactgttaccggcccaggacaagacaagaccagaagtt
gagagtcagcattgcaaaacttttagagtcatttttgtctgttgaatcta
ataataaaaaatgtgtgcttgtatttcatctcttcttcctcatatttcat
ttttattgcattgtacaaaagtatcagtctatgacagattgaagaggata
gaaattggtcctttaccccagagagtttgagaagcactgATAATAAggaa
acagcagaggtttagagaccagcagccctgctggtgttcgaatcctgact
ctatcacttactggtactgtaaacttggggaaattatttgacctccctat
gccacagtttccttgtagaatggggtgaataccatctacctcacaagCTA
GACTTAAGTGTTTCCCTTCTCTTAAAGGGAAAGAGAAGGCATGAAAACAC
TGGCCTCTGAACAACTGGGGTAGATCACCCTTGTTCTAGGCCAATAGTTT
TCACCCTCTTTCCCCTCAAGAGGTGGCATATACTCCCAGTGTGACaattc
tggttgccactttcttgaataagttatttctctaaggttccctttcctca
tctttaagtgtagattataccagcagggttactgtaaggattagatacaa

FIG. 3.18

gaatgcatttaaagcacttatcccaagattgctgcactgtaacagttcta
tCTTTGGCATTATCATTGTCCCATTAATAAATGCAGCTGGCCTCTGGGGC
AAGGGCAAGGAGGGTGCAACTTGTAAAGCTGCCCAGGTTATCTTGAAATG
CCTTCTTATGATGGCATGCCCCCACCATCACTCTAGATATTAGTAAAAGG
ATGAATCGTTTAGAAACTAACAGTTCCCAAAGTCCTTGTTGTATTATATA
CAAACAACATTTTTAGTATCTTAAGTATATATAATTTTAACTGCTGTATC
AACTTTAATCTGAACAGAAGATCAGGATAAGTAGTGTACCAATCATTACA
TATTTACAAACtaaaatttaaaaagaaaaaatatttaaattaGTTAAGAA
TATGTTTCCCCATTATTTAGCTGTAAAAGAGAAAGATCATAACATTCATA
CTTGCTCAAAGCGATAGGAAGAGAGATTTCCATTGGCGATCCCTTGTAAC
TTTGTCTTTCTCCAAGAGCATATTTGACTTCTTGTCCATTGATCACTACT
TTTTCTATTGTAAGGTCCTTTGTATCCAAAACCtaaaattaatattttta
aataGTAAGAAAATAGTTTCATTTACCAGAAAAAAACTCATATTAGATATA
GGCTACAACAACTAGTTGCTTATGGAGAGTAAAATACAGAGTGAAATTAG
AAGAATTGAAGAGTCAAAAGCTAGTCTAGGTCTCATTTTTTGGGACTCTA
AGCATCTTGAAAATTTTTGGGTTCTAAGATTTGCATATATATTGTTAAAT
AACCCTAGGACAGTCACACAAATTTTGGGCTTTAAGTAAAAGTCAAATCT
AAATCAAAATATGTTTGCTTCTGACTCCTAAAATTTTCTCTATTATGAAA
AACTTTATCTATAACTTAAGTTTCTTTCACTCTGGCTCCTCAATACATTA
CACAATATATTTCCTCCTAGAACTCATGTACTTTCAAACTTCATGTTCGT
TAAGCAAATCAGCAAACTGTATATCACTGTGGTTGTATATCTAGAAAAAG
CCCAACCTGGTATGGTAACTCAGACCAAATGATTCTGCAGAGGATTGGGA
GGCCATATCTACTTGCCATGGCCAATTAAGGACAACTGCTTTGGGCATGA
AGGAGTGACATCAAGTGTCAGAGTATTTTCTATCCCCAAAATCCTGAGCC
CTACAAATCATACTCTTTAATTATCTCTCAACTAATCTCTTGTCCTAGAA
TCTTGAACCTTCCTATGCCACAAGACTGTTTCCTAACAACATAAACAAAA
TTCTACTTGATGGATCTACCCACTAAATATTCTAGTTTTCCTCCTTCCTT
CCTTAAACTCCAAGGGAGTTTTTGACTGCTATGACTACTACTTCTACTTC
TTCATTAATCATCCTCCCTTTCCCCTTCTTCCATCTGGCTTCTTGCTATT
GAAAGGGCAGCCCCCACCCCGATCAACAAAGTCTTTTCTGTCCAATAACC
TTGACCTCTGTCTACTCACAGCCCTTATGGACTATGTCATCTGGTTAAAA
CCCCTTCCTTcacttctttgcctgtacgcatacatcataaatggttctct
atttgtctaatgtttttttcctttcccctcctttattccaattcaaaaat
atggatatgtcccaatgttccagccccggtcctttgattttcttgccata
tccttcactccctagctcttactcatgcccacatcttcaattagtatctc
tgtgaagatgcctgccattctagttctacagttgtattccctccccagga
cctcagtcgaatcgcctgctcaacatttccatgggacatagcaccacaca
ttgaataggcttctaaaaattccaaaaatgatttttatactccctgaatc
agatttctccccagatttcttgattctgttaaaagaactcttccagttac
ctaagGTTTGATCCCATTTCCCAACCCCACACAGCCACTTAAAAGTTGTT
CTTTCACAATGTCTTCATACTTTTCCTTTCTTTCCACTACTAACCCAGGT
CAGGCCCTGGACTGGCAGAACTGCTTTCTACCAGATCTCCCTACCTCTGG
CATTATTTTTTTCCTTTTCTGAAATCTGACCTGGCTACATGTGAGGCCAA
GAACCAGCCATTTCCCAGCTGCCCCTGGGTACTTTCTTTTGGGGGTACCT
CATTTGTTATCCTTACTCTAAATTAGTAGAAGATACGGTTTATATCTTAT
TTAAAATAATAGGGTTACTCCTTCATATTCTAGTACCTCTCTAGTCTCTT
CATAGTCTAGTACCTAGTTCTGAATAGCTATTCAGAATAGCTAACTTGTT
TTAAAAACTTGATTTGAGTATCTTGTGTTTATAACACATGCTTATATAGA
TGAATTAACTGGGTCATTTCCCAGTGGAACATATTCTGTTTTCTATATTG
GCTAAACTTTCCAAATCTGTTCAGAATCAGAAGTGTCATAGTGACAACTA
TTTTTTGTGAAACGTTTTGATATCCCCTGTGTCTGTTATAGctcttggcc
ctaccctttcctataatacttactgtactgcattataatgatttcttttt
ccattagactaagggttctaaaacagagaatgttacttaggtctgtattc
ccagggtttagcactctgcctcaaaaacactaggtgtcaattaatgCATG
AAGCAGGTCCTAGACCAAGAGAAAACAAAAAATGCAATGTTTAAGCTGTA
TTATCTCAAGTCCTAAGTCTCAACTATCATTTGCAAACTACTTTTTAAAA
TTCCCCTTCAAATTTCAGCGATGTTATTTTTAAAAAATAGTCAAAAACTG
TAATAAGAAAGAAAAATAAAGAAAACTGGATTGTTGACAAGTTGGATTTA
GTACTTTTTAAGAAACGTGTTAAGCATCAACAGCTCTACTAATTATAGGA
TATAATTTATATGTTTCACAGTATCCTCTTTGAACAATACCCTCCATCCC
CCTAAAAAGCAGTTGTACTTCTCAGTAGCTGGTCAGTTGACATGGAATAG

FIG. 3.19

GTATCTGATTCCTTTTTGCACAGGCTGGTAGGAAGCTCCATGTCAACCC
TGTGGCCCACTTCTTTTAAAGTATAGAGGGCTTTATGCCATGGGTTTTGT
TTCTCCTATCCCTATTCTCTCTTCCTGCaaattatttaattatttttaat
CTTATACTATATATGTTGCTTCAAGCAGTCTCAGTCCTTTCTAGAACAAA
GCAGAGTTTTTTTAAAAAAAGCTTTATGCCTCATTATGATGTCTAAATTT
ACATTTTCTACTTGCTATGTGCAGGGATATGATGAAAAAAAATAGGTTTA
TGTGTGAAACACAAAGCTAAAACTAAAAAACCACCTTGATTTGATTCCCA
GTTGAGACATTTACTTAGTGAAAACAAGATGGTTTGCAGTCAGAATTACC
TATTGTTAACTGCTGGCTTCTGCCTTGGCCATGGCACTAAAACCTCTTGA
GCCACTAACCAAAAGAACACCTAAACATTTCTGAAGGTTTCAGTGAAAAG
AAACAAATGTATGAAAGTTATCATAAATTTGGAGGATCAAACTTCAGTGT
AAATAACCCAAAACTTGAAAAGAATTTTAGAAAGCTTAGAATTTGTCCGA
TTAAGTCTCCTTCAGCATTCCTCAACATCACAAACTCTAAGAACGGAGAG
GAAAAGAAGACATGACGTCTCTCCTGATTCCGCACTGGCACTGGGTCTTC
CCATCTCACCTCTGAAATACAGCTGGCACTATTATCAATGTAGCCCATGT
TAAGCTTAGGCACTGTTTTCTAATTGAAAtcatccattaatcaaactttt
gaatgtcctctacatgccagacatagactatactaggaagctgagataca
aagagttatgaaacacagtctctacattcaagagtccacaatctagtgga
ggaaagaaacaagttaacTTTAAATAAATACTAATTAACTAATTAATAAG
GATAAGCTCCTGGTCTAAGGCTTTTGTCATAAATAAGCAAACAATTATAA
ACATGTTATTTTGTACCATAAATTGCCTTCCTTGTATAACATGTAACATT
ATTATAATTCCAGGCTCTAATTTGCTAAACAGACATGCCAACCAGAAATC
ACTATTTTAAAATCTTACTTTTCTCTAGATTTGGGGAATGTAAAAACAAT
GAGCAGATTTTTAGATTGGGACATTCTTTTCAAAATTTAAACATCCTGAC
TCTTGCTTACTTATAGAACAGAGATAAAGTTTTTATTCTACAAaagtgat
gagaacacatggatacacagtggggaacacacactggggcttactggagg
gtggagggtaggagaagggaaaggatcaggaaaagtaactaatgggtact
aggcttaatacctgggtgacaaaataatctgtacaacaaaccctcatgac
acaagtttacctatgtaacaaacctgcacatttgaagtacacctgaactt
caaataaTAAATTTTTTAAGTTTTTATTTTACAAAACAAAGGTAAGTGTG
AGGTCACATTAAGCAGCAAAAAGCTATAAAAATTTCATTCTTTTACTTT
TATCAGCATAGtttataatttaatttttttaaataaaGGTGAAGAACAAG
AACTTTCCAGTTAACTAAGAGCTTTGAGTGGGTTTGGGGCTTAGTCAAGG
TTTTATTATATCTTAAACCAATTGGAATATTTCTTCTGAAATATATGTTG
CAGCTAAAGATTCAAGGAAGAATTTGCTGTTCATATATTAGAAAAAACCTC
TTTAAATTTCTTCCACTAGCGACCTCGGTTTTGGTTTGCAATTATTCACA
TCTGAACACAAGTGTCCTGAATTGCTTAATTTTTAAATCTCTAGTACTTT
TGAATGTAGGACGTATAAACTCATGTTCAAATATGGCAGTCTCACAGTGT
GGTTTttcttttttttattattatactttaagttctggggtacatgtgcag
aacgtgcaggtttgttacataagtatacacatgccatggtggtttgctgc
acccatcaacccgtcagctacattaggtatttctcctaatgctatccctc
ccctaggcccctacccccaacaggccctggtgtgtgatgttcccctccct
gtgtccatgtgttctcattgttcaactctcacttatgagtgagaacatgc
ggtgtttagttttGAAACTGCATTGAAATAGGACTTCAGCCCTGCCCAGG
CAAAGTTGCTACTGCAATTAAAGATAGCATGGTACTTCAAGAAGACCAAA
GTGCGATCTGCAAGGAAATAGATGCCTTCCTGCTTATAATATCTTAATTT
TCTTTCTTATGGTACTTTTGTTGATTACCTATCAGTACATAGAGGAATCG
ACCTATTTTTCAAATCAATCAGTTTAGCAAAATGTTGAGGGATGAAGAGT
AAGAAAGTAAGTACTTATTAGTTCATATTAATGAAATCAAAATTCAGATC
CTTCCTACACAAGTAGGAAAAAGAGGCCTGAAAGCCACCAATTCTTATCT
GCCCGATCTGATCTGATTGCTTATTGATGTGCTTTAGTAGATTTCACCAT
GCTACACTGTGTAAAATACACATGTAGCATCCTGCCCTGGTGAAGAAGCC
GAATTTGGCTGTCTTTTCATGACCCTCTTATTTTTAAAATGATCTTCTAT
GAAATTCTTCAGGTGAAAGGTACCTTCAGATGAAAGGTATAAACCAAATA
CTATTGGGCAATTTGAGCAAGAACATTAAATATAGGTTATGATACAGATA
AAATCATTGAATAATATTCCATGAATCTACAACCTTTCTTCATTCCAATG
GTTATAGAGTTTGTAGAAGTATGTGTTTTCTAAGTGAAATAACTACTTGG
CTCCTTGGAACCAACTATTAAAAAAGCGTATTGAATCATCCTTAGAAAAT
TTGAACGTCCCATCCGTTCTTAAATTATTAGAAGAAAGTTGATAAGATTA
AAAAGTAGAAAGGACCCTGAAGAGAGAGAGAGCTGCGCCTAGAGTTAGCAAG
CAGGGACTGTTAGTTTCAAAGTAGGGCGGAAAGAAGAGGCCTGCCCGGCC

FIG. 3.20

GGGGCTGGAAATCCTAAGAGGCTTGAGAACGACTAGCAGGGAGATCCAGG
GAACTAGGAGGGAGACGGATGGGTGGTGCCCTGCAGACCTGTGGATTGAA
ATAAGTGTTCCCGGGAGGCAACCGTGGGATCAGGGATCGACAGGACATGG
GATCTGAGACTTGGGTGAGATTGTTGACTGAGGAAGGTGCCCAGGGGGCT
GGGAAAAGTCTGGGGCCTGAAGAAGGGGGTTCTGGCCGCAGGCCGAAGC
AATGGGGAGGCCATGGAGTAATTAGAGCCAGGAACTAAAATTATGGGGGC
TACTGCAAAGATGACACCTAAGGGCTGGGTGAGTTGAGAGGAGTGGACGA
GGCGCTGGATGTGCCCAGGGACCTCGGAGAGAGGATCCAGGCGAGGGGCG
GAGGAGACATACGTATAAGTGGGGGCTGAGGGAAGGGATGCAGAGGCGTA
AGCGGGGTTGAGAAGGGGTGCTGTGAGAGATCTGGGGGCTGAAGTGCACA
ACATGAGTTGGATGGAGGCTACAGAAGAGCAGACGGGGACGTGGGGCTAG
GCAGGGGCCGCGGCGGGGTGAGCCGGAGATCCGGGAGCCCGCAAGGACTA
GGGTCGAGGGGCAGGGAGCCCGGGAGAGGCGGGCACTGGGCAGGCGCCCC
ACTGTACCAGGCTGCGCAGATTGTCCTCCTGAGACTGGACCGTGAGAGCA
GCAGTCCCGGTCAGCGTCCGGCGAGTAAAGTCGACGCTGCAGCGCAGGTG
CAGGTGCTTGGTCCGGCAGACGGAAGCCGGAGAGGCCAACGAACAGGTAT
CCACTATCTCGGGCATGGCTCTGGGGGATCACACAGCACAGCGACCTACA
GCCCAACGCTCAGCTACCAGACTCGTCGATAGAGAACCTGAGGAGGAGGG
AGAGAGGTAAAGAAGAGGAGGAGGGATTCGCGGTGCACGCCGGGAAAGGA
AGTTTCTTAAAGTCAGACGAGCGTTGGGGGATGGGTGAAGGAACTACAAG
TTCCATGGTGCCGCGCGGCAAGCGGGCGCTTGGCTACCTGGGAGCGTGTG
TGTTAGGGATGTTGAGGGGGACCAAGCGTGCTCCTGGAGCTGAAGAAGAG
GAGGGGAGTAGGGGCAGTTAGAAGGGTGGCCGAAGGGAAATGATGAGAAT
GGAGGGGGAGATAAAACTGAACACTACCATTTTGGCTCTGTTCAACTTTC
GTGGAAGCTGTGGTGGCAAACGTAAGAAAATCAGGTTCATTGGTGTTTGC
ATATAGCGAGGGCGGGGCGGAGCAAAAACGTAGAAAAGGCCTATCAGAAG
GCTTTCTTTCGTGCGGTtcctcgttagtatagtggtgagtatccccgcct
gtcacgcgggagaccggggttcgattccccgacggggaggcaCAGTAATT
GTTTTTTGTTTTTAGCTGTAAGTAATTCAAGGTTTAAACAGTTGTTTTGT
CAGTTTCAGTGTTTATTATGTATATCCCCAGAACCTGCATCTCTCAAACG
GAGAAAGCCAACATTCCCATCTTAGAAACTAATGAATTTCTATAAAAGTT
ATGCACTGGTCGCAATGGGAGTACAGAGCTGGGACATCTAGCTCAGCTCT
GGGGCCTTTGTGGCAGGTGAAGGAGGATTGAAGGATGCCTTGCCTTTAGG
GTGGGGCCTCAAAATTAAAACTGGAAAAATTGGAAGAGGCTAGGTTTCGA
AGGACCTTAAATAGGtggccttttaatcctgggtgcattaatgggggacc
cactgaagagttttcagcaggcgactgataaagcatggtcagactcatgt
tataaaatgcggtatcaaaaccattagcaggagatttaggaaactattaa
aatggctcaatcagaagatgctgggggcctgacataggtaagtagtaagt
taggatagagaggaaggaatgaatagaaggaatacttatataagtggatt
cacagattgagaggagacgaaggtggcccaggctttcggcttcagtggct
ggctagtcattaaccagaggtagtagtctatatgaagaggacagtatgtt
aggctgtacttgcattgctataaatacctgagactgggaagaaaaggggt
ttaattggtttacagttacgcaggctgtacaggaagcatagctccagtat
gcttccaggtaggcctcaggaagcttacaatcatggcagaaggtgaagaa
ggggcaggcctctacatggcccgagcaagagcaagagattgcggggccgg
tgccacacacttaaacaatcagatcccacaagacactgtggcgaggacag
caccaggccatgagggctctgccccccgtgacccaaacacctccccaccagg
ccctacctccaacactggagattataattcaacatgagatttggtaggga
catatattcaaactaaatcagacagatttaaggggaagatgctaaattca
attttggacatatgaaatttgagaacctatgggagtggaagtggagatgt
ccatgagtcacttggatatttaagtccacagctctggggaagtgccaggt
agacatgaccacgtcacataacgtggtggatgaaattatgacagtgggta
agctcaacccaagaagagtgtgtaaagagaagggtaatgaaaacaggttg
gaagctgagagaacaccagaatttattgttttaaaaagggctagaggaag
agaaacccatgaaataaaccagaaagagcCAACCAACAATGCCAGATGCA
GTCCCGAGGACCACCGAAGTAAGAAGTGAAAATTCTCTAGATTTGGCAGT
GGGGTGAGAATGGGGAAGGTGGTGATTTTGTTGACTGTCGTGATTTGGTT
GAAGATGGAAGCCAGAGAGTAGTGGATTGAGCAATGAAGAGAAGAGGGAG
GTGAAGCATAAACCACTGTCAAGTTGCTTGGCCAATGTGAGAAGGGAAGA
TAAAGGGGAAGCTAGAGAGGAATGCAGCATTGAGAAAGCttttttttttt
tttttttgagacggagtctcgctctgtcgcctaggctggagtgcagtgg

FIG. 3.21

cgcaatctcggctcacacaagctccgcctcccgggttcacaccgttctcc
tgcctgagcctccaaggactacaggcgcccgtcaccaagaccgactaatt
ttttgtgtgtgtatttttagcagagacggggtttcaccgtgttagccagg
atggtctgcatctcctgacctcgtgatccacccacctcggcctcccaaag
tgctgggattacaggcgtgagccaccgcgcccggccGAGAAAGAATTTTT
TTAATGTTTGCTTTTTAAGGCAAGAGAAAACTTTAACATGTTTAGATATA
CAGGTGAAAGGGCTTCTGGAGAAGAGGAAAGTTTCTGCAGAAGGATCGAC
TCAGAGGCAAAAAGGTAGAGAAGAAGAAAGTAAAGATTTCAGAGGTGTGA
GGGATAGTTGATGGGTTTAGCATGCTGGTATGGTTCAATTCTCTATCAAA
AGTGACGAAATTTAGCTCCAGCAACAACAACAAAAAACTGCTATATTTCT
GGATATCCTTGTGTTGGCCCCTGCAAGCCAAAGGAAAACAAAATAAAACC
AAAAAATCCCAAACTATGAAATCTAATACCTTACACATGCATAGGTCCTA
ATTCATAGGGTGTAAGAATTTGTCATCAACATTTGCATTTTCGGATTTTT
TTGGCAAATGTCctgttgcccaggctggatacagtggcatgatcatgggt
aactgcacattcaacctcctggactcaagcgattctcgtgcctcagcctc
caagtagctgggactacaggcgcccgccaccacgcctggctaatttttat
atttttttagagatggggttttgtcatgttgcccaagctggtctcaaact
tctgagctcaagggatccacctgccttggccttccaaagtgctgggatta
caggtacgagccaccacacAGAGCCGCAAACATTTTTTGAGGTCACCAAA
TCTAGGGTGACAAATACAATAGATAACATAGAATTCATTTAGTCAAATAA
TACACAGTCAAATCATCTTATTTATCTAGTATGGAGAAAGGATAGTTTGT
TTTAATAAGAACGTCATTATCATCATCTTCTATTATTGATTACCAGGAAC
CCACAGAGTTTATGCCACTTGTGTTTAAATAAAAATATCCACACACAACC
ACAAATAAATTCCTCCATTAATATATTCATCAAAAAATAAATTACAGTAG
GAATTGTTTTCTGAGATACCACTCACCCCAAATATAGAATGTACAAAATT
TGCAATTTACAAGCAATTGGAGTATTATTGATATCCAATGGGGAATTGAG
AATGCTTCAAAAAATGAGGCTTTCCACTGCATCTATAAAAGAAGGGTAAG
gctgggcacagtggcccacaccggtaatcccagcactttgggaagctgag
gcaagcagattgcttgagcccaggagtttgagttcagcctgggcaatgtg
gtgaatccctgtctctacaaataatagtaataataataataaAAGAAGGG
TAATATCAGGGTTTAGTTACCAAAGGAGACTTAAAGATGAAAAGATGATC
TATATAAAATATTATGAAAAGAAATAATACCTATATTTATAGAGCCATAT
GAACAGGAAgaattccagccctgctattcacctggaaaagttacttaatc
cctcaatcccctcaggataattgaggcacctgtggcccgtgcagttgttg
aaaagatgaaatgagataaagtatgggaactgcttggcactgtgattgaa
acagattgggcatttgttacatgttagctAATATGATTATTGCTGTTGGC
TTTTGTCTATTTTAACCACTGTAATGTTATTTTTCCTTGTTGTGTTAGCA
AGAGCTTTTAGGACAACCTGGGAAGTGAGAAGCAACCACGGTTTGTACAG
CAAAACAAGTCACACCAAATTAGGCCTCTAAAAAGGAATGGCAACATTAG
CAAAGATATGTTTTGAAATGCATTTACGGGAAATTTCAATTGTTGCACAA
ATGCTTCCCTTAAAAGGGCAAAAAGACTTTACATTGTTTTCTCCCCTTCC
TTTACATATACCTTTCCTTTCTTGAAATAGTCGATGTAATTTGCAGATAT
TTATTAGATGCATTCTACTACACTGTGCTACCTAGAAAATAATTGGGGAA
GGTTCTGTCTTACCTCTTGGATAATTTATACTCTAGTACCCAGCTGTACT
AATGACCTAAGACAACATGGTGTTAAGAGGAGACTAAGGCCCTAGAAAAA
CTATACATGAAATTCTAGAGGGACAAGTTCTATCCCTTTGGAGAAAGTCA
AGAATAACGTCATGATTAACATAGCATTTGAGATGGGATTTGAAGGATGA
GCCGAATATTAATAGGAAAAATGGTAGGATTGAGCATGGGGAGTGGGAGG
TGGGCAGATTTTTCAGGTGGACTTAGCAGGAATCAAGGCGTGGGGCCAGA
AGTAGAGATGTGTTTGGGAAAGAACAATTCTGAAGGTACAAAGTCCTACA
AGTTAATGCAGTGCCCTCACACACTCCTCAATAATCTGCCTTTCTTCTTT
CCTCTCCAGGTTATACATCTGGCAtgatagagatcattagttgtcttcta
atacctatatatcttttcatccttagtagtaaaaccttccatgtttagct
ggacacatggccacccggaagtagacatttcccaaccttctttgcagtta
ggccataccattaagttctgtccaatggcatgtaagtggaattgtcaatt
atgactcccaggaagtgtccttaacagtaactttattttctttttaacct
tttctctattcttttcctggaatgtagataagatacattgatggctagag
ctctgactaccatgttgtatcatgatgttggagccatgtgctgagagtgg
tggagcagcaaggtagaaggagccatgagctggaaatagccaggtctctg
gggatcatggaaaccccatgtgaactgctctgaatttctcaaagaaataa
atttctactttgtttaagacagtgttatcttgggttttctgtccttcaca

FIG. 3.22

gggaactcaatctttactaagacTCCTGGTCTCAGTTGGGTGAGTTTATC
AGTTTTGCCCCAGATACTTGCCCTTATCTGTTGGTTTTCCACCACATTAT
CGTGGACAGATCTTTCTTCCTTCTTGCTTGTGTTATCTGCTAGAGCATTC
TTTCTAATGTAATCATCTCACTCCCCTGCTTAAAATCCTTCAAGGTCTTA
CTAACATTGCCAGTTGATATTATCTGCCTTTTTTGATTTAAGGCCCATTT
TCAAATACTAGAATTTTTGGCATACAATCCAAGGGATTAAAAGATGAACG
TAAGCTTTTTTTTTAAAGAAAGCTTTGGCAAATTTTTTTTAAATAACCAG
TTATTCACAGTATATTATAATATTATATTTGTATGCTTTTATGATTTTTT
AAATCTGAAATTATATTAAAATGAAAGATGAGTCTCATTTCTTGTATAAG
TTCACTTTTTTGTTGTTGTTGTTTTGGCATTTGATGTTTGTAAGAGTTGA
GAACCCTAATTTCTGAGAAATGACATGGAAGACTGCAGCAGTACCTCTG
GACTCCACAGTTGGGTGCTCTTCGAGACCATGTTGCCATTTAAACAGAAT
GGTTTCCTCCCTTTGCTCTGCCTGCTGATGTGGTCTAGCTAGCTCCTGAT
TAAACTCTGCCTCTTGCCTCTTTTTTACAGAAATGTGTATCCTCtacatg
catcaaaacatcacactataccccataaatacatacactttttatgtcaa
ttaaaaaaaaaCAAAAAAAGAAATGTGTATCCCCCTTTACACCAAGTTA
AATCACTCAGCTTATTATCTTCAAAGTAGTATAAACCCCCAGTTGTTGTT
Gttttgaggcaaagtctctctgtgtcgcccaggccggagtgcagtggca
caatctcggctcactgcaagctccgcctcccgggttcacgccattttcct
gtctcagcctcctgagtagctgggactacaggcgcccgccaccacgccca
gctaatttttgtatttctaatagagatggggtttcaccgtgttagccag
gatggtctcaatctcctgacctcgtgatccgcccacctcagcctcccaaa
gtgctgggattacaggcgtgagccaccgcgcctggccATAAACCCCTAGT
TTTAAATTAAACGTTTCTttttgtttttttttcttttttttttttttttt
gacagggtcttgctttgttacccaggctgaagtgcagtggcacgatctca
gatcattgaaacctctgcctcctgggcgcaagtgatcctccacctgagcc
ttctgagtagctgggaccacaggcacaagccactacgccgagctaatttt
tgtatttttagtttgtttgtttgtttgtttgtagtgacagggttttgcca
tgttgcccaggctggtctcgagctcctgagctcaagcaatgtgcccatct
cagcctcccagaaagtgctggtatggcaggccaggtccactaacgcaggc
ctccataacaactgtttcagtactgactgagtggttaaattaaatattaa
aatccagtacccttatgcaaaggctggaatgtaacaaaagcccaccaaga
gttttgcctaggcctttcctgaaccttaaagcatgattaaacaagtttat
tgggagtctgaaggaactccccaaacctccatgatttagcaggagacaag
ataaggataatcaccccagcacctgcacccatttagattaatttactgac
gctccacaggaaggtcttcaagactcagaccttagttatagacggaaaga
agttaatcacctacgtctttagatgaatgcacacttacatatagacatat
agcttagaaggtatataagctctggaaaactttgtaattttgagttggtc
tggtgataatttccaggccttctccttagaaaaaaataaaggtccctatt
cctgtaaccggttacagaaataaaaactcgcttcctccccagttcacctg
catctcattattgggccacgagaaacagcagcctgaccctcactttggtc
caagaacactgggattacagacgtgagccaccatgctcagctAAATCAAA
CTTATTTCTATATATTGGTCCACAGCAATGTTCATGATTGATAAATGACC
AGTCTTACTGTGGCCACCAGGTCTGTCAGGATCTTGATCCTGCTTACCAT
TCCCATCTCATACTTCATTCTTCCCCCAAAGCACTCTGTCCTTGGACTGC
ACCTTCACATCAGCCTATCTCACAACTCCACTTCTTCGCTTTTGTGTTAT
TTCTCCAGAAACATGTTGCTCCTCTTTGCTTTCTCCACATTCTGCCTAGA
AAACTCCCTGACGCAACCTGCAGTAGTTGGCAAAGTGAGAACATGTCGGG
TAGACCCGGGAGGTGAATTGAAGGGGTAGGCAGGGACTCGACTTGAAAGA
ACCTCACATGCCTTGAGAAGGAGCTTGGAACTTACCTTTAAGGCTGCAAG
AAGTCGACGAGTCTTAACTGGGATATGCATGGTCGGTACTTGTCTTTTAG
AAAGATTTCTCTGTGGCAGCATGGGAGACAGATTAGAGGAGGTGTAGACA
GGAGGAGAGAAAATAAACTCCCAAGCCCATGCATCCTCTTGCCCTCTTCC
CTTGTTGCTTTAAAAGACAAACATgcgcctgtagtcccagctactcggga
ggctgaggcaggagaatggcgtgaacccgggggcggagtctgcagtga
gctgagatcgagccactgcactccagcctgggcgacagcgagactccgtc
tcaaaaaaaaaaaaaaaaaaaaaagacaaaCATGTAGTTCTTTTCCATT
TAGAGAGTTTTATTGGTGATTATTATAGGAAAACAGACTGGAGAGAGAAT
AAAAGTAGGCGCTgcagcaattctcaggtgagagatgatggtggcttgga
cccaggaatcagcagtagaattggtaagaagtgatcaaattcagcataaa
ttttgaaggcagacctactaggatttcttggcagtttagatatggagtat

FIG. 3.23

gagggaaagggaggagtcaaagataatgccaagacttttgacctgataaa
ccaggaaaatgtagtaggattagctgagaaggagagattgtgggagaagc
agactggagtgggcgagggtaaattcaggagtccaatcctttttttcccc
ttaattttatttacttatttatttagagacagcggtcttgctatgttgcc
caggctggtcatgaactcctggcctcaaaccatcctcctgcctcagcctc
tcaaagtggtgggattacaggagtgagccactgtgcccaactcaatcttt
cacatattcaatctgaggtgtctgtgattcgagtggaggtgctgagtagg
cagttggacatatgagtatgagtccagaagaaaagctggaactgggctgg
agatacacatttgggagttcagcatgtggatggcacaggggggaagaagag
acgctagctatggagactggaaaggaatggcctcgatgaagaaggaaaac
caaggaagtccgtgtcttggatgacaagtgaCATCTGGAAAAAATAAAGGA
GCAGTGTGGTCAGGGAGCCTGATGAAATTCTGACTATGGATGACTCACTG
TTTTGTGTAAAAAGGGGGAAGAGAATTTATTCTAAAAATTTGTTCATATC
TACATAAAATACTTCTGGAGGGATGCTCAAGAAACTCATGGTATTGTTTG
CCTGTGTGGACAGAGAAGGAAGGCCAAAGAACAGAGGTGAAAAGTAGATA
TTTCAACTGAATAATCTTGTAAGCCTTTTGAATTTTAATGTGAATATATT
TCCCAGTCAAAAGGTTATTTATTGATATGAAAAAAAAATAAAGGTCACTGG
AATCCCAAACCACAAACAAAAACAGCCCTTGCTGACTTCCTGTGGACTTC
ATAGTGTCTACCACTGGCCCCGCGGGGCTCTGCAGCTTCCACTTGAGTGG
CTCGATACACCCTGCGTCAGCCATGCTGAACCAAGGTGTTCAAGCTCTCT
GCACTCTCTGGCCCTTCCTTGAGCCTGCATGCCCTTCCCACTCCCACTCT
TCCCGCAACCTTGGCAGGGCTCTCCTCCTCCCCTTCAGGACTCTGCCCCC
CACCACCCTCCAGTCTGGGCTAGAGTCTAGTAGAATCTCCCTTGCTAAGA
GAACAAGGTGCATGTGACACCCTTCTCTTCCTCCCTTCAGTGTGTGAGCA
AATAGAAGAAATGATTTAGCCACATTTTTAATGTTCACCTTACAACATA
GTTGAGGCAATCCTGACCAGTTTCTCCATCTTCTGTGAAATTTCTTCTTC
CTTGTGCAGCCATGCGCATGAATTCTATATTTATAGTCACATCTCCAGTC
TGTTCTGCATGTCAAGAAAAGGTTTGGgactgggtgcggcagctcatgcc
tgtaatcccagcactttgggaggccaaggtgggcagatcaccaggtcagg
agatcaggagcatgttggccaacatggtgaaaacccatcgctactaaaaa
tataaaaattagccgggcgtggtggcgcacacctgtagttccagctattt
gggaggctaaggcaggagaatcacttgaacccaggaggcagagattgcag
tgagccgagatcgcaccgctgcactacagcctggtgacagagcaaggctc
catctcaaaaaaaaaaaaaaaaaaacaaaaaCCCAAGGTTTGGGCAGCTG
GGAAGGCCAAAATGAAAGAAGCACGAGAAAAAGTTCTGCCAATTTTGTAA
AATAGCATAAGTGGTCTCCTCCCAGATGCCTTTCTGGCACCCCACCCCAC
CCCATGGTTGACCGCAGGCAGAGTCTGGAAAGCCCCACAGCCACCCGTGT
TTCCTCCCACACAGTTCTGTCTTTTATTTCTCGGCTTGTGTCCTTGGGAG
GGACTGGCCTGAACCAAATAGGCTGTCACGCTGTCCTGAGTTGGAGCCAG
ACAGTGCCAACCATCACATGGCCTTCTCTCTTAGGTCTCAcaaagtgtgt
ttgaagatcagcagcatctgcacctcctagaagcctcatcagaaatgcag
atcttggccgggtggctcatgcctgtaatcctaacactttgggaggctgt
ggtgggcggatcacttgaggtcaggagttcaagaccagcctgaccaacat
ggcaaaaccccgtctctactaaaaatacaaaaattagctgggcatcgtgg
tgtgcatacctgtaatcccagctacttgggaggctgagtctgaggcatgg
cgtgcacctataatcccagctccttggtaggctgaggcaggaaaattgct
tgaacccaggacgtggagtttgcagtgagctgagatcacgccactgcact
ccagcctgggtaacagagcaagactctgtctcaaaaaaaaaaaaaaaaat
gcagatatcaggcctgccctgacctactggatcagaatccacattttatt
cagatccccaggagatctgtgtgcattttaaatgagaTCACTGCCTTAGA
GGCTCAAGAAATACTTTTGGCATTGGAGAAAATTCAGTCCAAGTGTTAAT
CAAACATGTCAGGACTCCTTCTCTTAGGGTCCACTGCCCTTGACCGCCAT
ATCAGTACTCTCTTAATACCCTAGTGTTATCCTCAACAAAGCATTTACCA
CACTGCATCATTGTCAGTTTACTTGTCAGCCTTCCCTACTACATGGTGGG
TCTTTAAGACCCTGATTGTATATTCTCCCTCTCAGCACATGTCTGTTGTA
TGAATGAACAAATGTATAAATGAGCGAATGAGATTTCACATGAGGTTCCA
GGCAAACTTTTATTCAGTGTTTCACTCTGTGTTGACTTTGCAGCAAAGAA
AAAGCCACCTTCTGCACTTGCCCTTGTCCTCTGATGTCACCAGGCAATGT
TTGTTTGTGATACAGAATGCCCTTGCCAGCCCACCCCCCCACTAATTGTA
AACACTTTTAAAAACAttgttattgaagcatactatccattcataaaaat
gcacatattgtaagtgtatagctcactgaactttataaactgagcatgcc

FIG. 3.24

agtgcaatcagcacccagatcagagacagaacattaccaccactgcactg
ttgcctcccttaagttccgtttcagtctctataaatcctgcttcctaggg
gtaaccactgcctgacttccaatagcatattaccttgacctgttcggcta
tttatctttcctttgcataaacagacacatacagtatattctgtcatgcc
tggctccttggctcaacattcctttgcaagatttctccataatgttgtg
tgtacatctaggctgtgcacactcactgctgtacagtgttccatgtgtgg
atataccatgatttacttatcctttcaaccgtggatagacatgtgggtga
tttccagttctgagttattattatgaatggtgctgctatggatattctgg
tacgtgtctttcggtgaacacatTGTAGCCAGGTTTTGACATGCTGCTTT
GAAGTTTAGACAGTTGCACCCTGCCAGGAGATTTCCTTTAAGACCCCTGC
ACCAGGCCAGAAACATTCACTGCATTGCAGCAACCTGATTCTGTAGTTGT
TGACACAAATCCAACACCCTTCTCCCTACCCCAGCTTGGGTAGGGGTTAA
AAGTAGATGAAGTAGGGAGGGAAGCTGTTTCAAGTTACAAGAAAAAGTT
CTTTACAACTGCTGGCCTTGTTCATACTTTATTTTCCTCTCACTCACTTC
CGTTTCTTTTCCAGGTAAGCCTGATTGCAAGCTTCATTGTACCTGTTTCT
TTCTGACTCAGATTCCAGCTCAGCTTACATTTTTCCCACTAAGTAGGCAG
TGATATTTCATCACAGCAGGTACTTACACCTTTTGTTCTGATGACTTAAA
GCACAAGTAGGTTTTGATAAGTGCTTGCAGGGTTTCATTTTCAAAAGTCC
TATTTCTGTGTCATATTTGTTGGCTTTGAGCCCAGTTTCTCTTGCTCTGC
CAACAGAGCAGGTTATGCCTATTTGCTCATGGAAATAACATTTTCATGAG
CAAAGGCTAACCCCAAATGCTTTCCTCCTAAACGTTCTTCTCATCTACAA
ATCCATGTTTGAGGAACTATTATTTTGTCATTTCTTACAAAAGGTTTTTA
TTTGAAATTCAGAGTTGAGTAAACCCATGGAAGAGACTCACATGGTTGAC
TCACTCTCTGCCCTCTCCTGCACATGTGTCTCAGGATTTCTTAAACCCAG
CCGAGCACTTCCGCAAACCTCCCAGACCTGACCTCCTCCTCCCTTCCAAG
CTGCTCCCCTTGGCTTCCAAAGCAGCCCCCTTCTCCTTTCTTCCTCACAC
ACACACTGCACCCCACTCAGCTCTATCCAACCAATGCACGGTCCTGGAAG
GCCCTCCATACCCACTTCTCTCACCTCTGCTCAACTGCCCCCTTTCGCCA
TAGATATATTCCCAGTGTATTTTTCTCTCTTTTGGTTATTAATTCTTCTG
AACATGAACTTCACATACCtatgtatgtatgtatgtatgtgtatgtatat
aCACATACATATATACATGcagttaatcctcattattcatggatttggtg
tttacaagtttgcctacttgccaaaatttatttgttattccaaaatcaat
atttacagagcttttgtggtcactcttggacacactcagagctgtgagaa
atttgagtctccggaggcacacagtctcaactgaggttaaacaaagtgac
cctctgccttcctgcttctgcgcttatactgtaaacaagtgtccttttg
cagtctaatgtcaccttgtttacacatttttgtgcttttcgttggtgatt
ttgcagtttaaaatattccccaagtgggtgctgaagtgctgtccagggtt
aagcgcaagaaggctgcgatgtgtttagggacaaagtgtgtgtgttagat
aagctgcatcaagcatgagttacagtgctgttggctgtgatttcaatgtt
aatgaatcaactatatattacaaaagtgtcttgaaacagaaaaacatata
caatgagattttgtattgattgatgaaaatgtgaacagaggctctcagga
acctactatatttcccctgggagcaaaggttcaggattcactaatgcaat
gtttatgaactttctaagatataattactgcaaatcatgagaatcgactg
TATATATTTCTTGTCCTTCTGGTTAATTTGTATTTGTTTCTTTATACCTT
TCTCACTCTGTTCCCAAAGAAGTGGAGAGGGGCAGTTTCTTCCAGGTATA
CCTTACAATTCTGTCGTCTCTATTGCAGCCCCCAGCTCAGTACAAACAAC
ATAGTAGGTCCTCAAAAGATTCAAaaggaataaaagacaggagtggagaa
aggaaggaacaaaagaaggaacgatggcagaacgaaaagaCGCACCATGG
AAGCTGAGGGTGCTGCTTATCTAAGCGGGCGTGGCTTCCCAGAACTTCTC
ATCTCTCACTCCTTAAATGCTTCCTCTTTATTTCATTGAATCATTGAACT
AGAATAATATAATATCAGAAATCAAGTTATATTTTATGATAGATTTGGCT
TTTTCTGCTGCTCTTTGCAAAATCTAACAAAACAAACCTTCCAGTTTCTT
TGATTTTTTTTTCAAACTTTTCTTCTCCCTCTCCTCATCCTCTACTCCTT
GATCTTCACTTGGAGAAGGACAATTCTAGAATTCCTGAACTCTAGGCCAA
AAGGAAGTGGGCAATCATGGCAAGCATAAACACATCCATGGCAAGTTATC
AGACACCTTTTGTGGGTACTAAACAGCAGGGATGCCCACTTGTCCCTTGG
AAGTTTGCAAACATACTGGGAAAATGGGGACTATAAAATTAAACCACCAA
AGATCAGTGTGGGAGACTGAATAATTAAAGGGTATCCAGGTGGACCAGTC
ACAAACGCTGTAGGAGCTCAATGGAGACATCAGTGGGCATCTTCCTGGAA
GCAGTGAGGCTTGCATGGAAATAAAAAACAGGGGGTTCTAATTTTTGTTA
TTGTTCACCAATATCAGCAAAAAAGGTGGGCACACCCTCAAtaaatgttt

FIG. 3.25

gcaaattctttacatgtgctaattaatcatatcttaagatgcaaaataca
ttgagggcaaggtttactcttaacaatggtcaatgtaaatccttacttta
aataagcatcttataattatgatttgcatggggggcacattttgtcagat
cttatttgtcatcattattttgttttgtttgttaatacactcatcttatc
ttggagtaggagaattattaggtctgttaatctttcttgttgctcactGT
TATTTTGCTATGGCAGCTCAAGCTGAGACAgaaattggtaccaggatggg
tgctgctataacaaatgtataaaaatagcaaagacgtggaatcaacctag
gtgcccatcaatgatggattggaaaagaaaatgtggtacatatacacaat
ggaatactatacagccataaagaagctgtcctttgcagcaacgtggatgc
agctagaggccattatcttgagtgaattaacacagaaacaaaattaaata
ctgcatgttttcacttataagtgggagggagataaacacagggtacacac
aggcataaagatagaaacaatagacacaggggactccaaaaggggaaagg
gaaggagggaggaaagagagttgaaaaactacctattgggtactatgttc
atgttcaccatttgggtgacagttcagcagaagcccaaacctcagcatta
ggcaatatattcatgtaacaaacctgtacatgtacctcctgaatctcaaa
ttaaaatAATACTACTACTAATAAAGACCAAAGTATTTCAGAGGGAGGAA
GAATTTGCATGGTGAAATTTGCGTAGTGAAATTGGCATCCATATGGTGCA
TAAGGGATATCTTTGGATCTTCTGAATTACATTATATACATTTTTTAAAT
TAAaataaattctaaaaatgtggaagcagtaatgatgcagggtgatgggt
gaaggctaaaagagttttgagatacatgctacaaaaagccaaggttgctg
tgaaaaaattgctaaagatgattctggtgaggactcaaaaagagcttctg
tcttccttctttgaggatgcgtaaacaatcgtgaacagaatgctagcaga
aatataggtggcaaaggctattctgtgaggcctcagatggaaatgaggaa
catgttattggacaatggagaaaatcctttttataaagtggcaaataact
tactgaattgtttatgttctagtgttttgtggacggtagaactttcaaac
aatgaaattggatagttggctgaggccatttctaagcagagtgctgaaag
agcagcttggttcctcttgaccactgatagtaaaatttaagaagagagaa
atgaattgaagaagaaattgttaatcaaaaaataaccagcacttaaagat
ttggaaaattcttagcctgtccttactgcaaaaaaaatgagaaaccatgt
tcagaagagttaggccaagcatggtggctcctgcctataatcccagcact
ttgggatgccaaagcaggcagattacttgagctcaggagttcaagaccag
cctgggcaacatggtgagaccccatctctatttaaaaaataaaaaaaga
aaagaaaagaagagattattaagagtgtggctggtcacccatttgataag
gagagtagtgtcagtatcaaccatggacctaatcagccatctcaacagaa
gccagaaatagagttgggattattccaggagaaataatgctttagtcccc
tgccagttgggactaaaaggaaaagagaaaacaagatggaatgaagtaag
gctgtgaatatgcaatccccttcaggaaaagagaggaaggatcccaaagg
caattcagacatcatcagggctgctactcccaccacaggcccagagtgga
aaggcccctgggaacaaggctacctccatcttggtttcaaagagtgggac
tgctactcagcactcatgtgggtgtggccctcacagacagccatgtgggc
agtgctacactgagctgaagaagcagggacaccccactgaaagatggggg
tgataccttccagtggttctggaagggaggaccaccaccccagtgggcct
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gcctaatgaagtttgacttctagattttggatttcttggtacttgtcacc
cctttctacctttcaatttctcccttttggaataggaatatctatcctga
gcctgttccatcattgtatttcggaagcacataacttgtctggtttcaca
gattcacagttggaaaggaattttgccttagggtgaattttgagtctcac
tcatattggatttacatgatatttagatgagactttaaactttagagttg
atgctggaatgagttgacttttgagactgttaagatggaatgaatgtatt
ttaaatgcaaggaggatgtgaattttgagagggacaaagggcagaaTATt
atgaactaaacgtttaagtctcccccaaattcatatattgaagccctaac
ccccaatgtgagggtattacgaggtgaggtctttgggaggtaattaggtt
tggatgaggtcatgagggtagatcccttgtgatggaatcagtgcccttat
aagaagaagagagactagagcttcctctctctgccatgtgaagatacagc
aagaaggtggccatctgcaagccaggaaaaggggccatggcaaacactga
atctgctcacagtctgaacttgaacttgtcagcctccagaattgtaagaa
atgaatatctgttgtttaagccacccagtctataatattttgttttggca
gccttagctgacccaggcaCTCACTTATGCTTACATTCTAACTTCTAAAT
TAAGGCTGCAATATATGAAACATGATCATAGAACTTGTAATTATCTGAGG
ATCCAGAAAAATCACGAGCCTGCACAAGGTTTATCCAGAGGCAGAGGAAA
TACCAGTTCACTGAGAAAAATTAAAGGGACAGTAGAAGAATAAAATATAG

FIG. 3.26

TTGTTTATAATTGTATGTTACAAATTATGTTTGTGAAGCCAGTTACATAA
ATAATCTTAAAGATTTAATAGTTTCTGCCTGCATCCAAATAATTGCCATG
TGCCTATGTCCATACGCCTATGTCCATACTACTTTGGAAACCTCTAATGA
ATGAATGTGTAAAGTTTGGATGGGTATTTGAGAGGGAAAATACTTCTTAT
GAGGTTGACAGTTATAAGCAAAGTTAGGAACAAAAAGCAAATTCAGAAAA
AAACTCATCTTTtgttatggtctaaatgtttgtgtcaccccccaaaattta
tatgttgaaatcctaacccccaagttgatggtattggcagatggggcctt
tggtgaatggaatttgtgctcttacaaaagggacttcagagagcttgtat
gcccttccaccatgtgaagacacaggaagaaggcaccatctatgaaccag
aaaatgggccctcaccagacatcacatctgctggcatctttatcaaggac
ttctcagcctccaaaattgtgagaaataaatttctgttgtgcataagcta
cccagtctatggtattttgttatagcagcctgaatggactaagacaCACT
TATTGAACCCCCACGTGTTTTTCTGAAGAATGAATGCCTCACATTTTACA
CAAGATGTCTGTGTGCACTGGGGCCGTCTAGTCTACCCTGGCCTGGTGAT
CAGGGCAGGGAATCACTGAAGTTTCCCATTCTCTAAAAGTGGAGGAAATG
GCAGCCATGGGGAAGCTGCCTTCTGCTAACACAATTGagccgtgaaaaca
atatacaactatttttgttatattccagtggtcacacagagcaaccccaa
tacaataggagggcacaccacaaagccatgagtaccaggaggggtgatca
ctgggagactccttggaagctggctgccacTGTGAGGCattatctctgtt
tcacagaggagaaacagaagctccaataaataattgctcaagtcaactca
acttggaacaggcaggtctggggttcaaacccagacaatgagaccccaga
acacatccttttagaacactgccctatacCCTGGCCTCACCACAGGCCTT
TTTTTCTAACTTCCTCTCTTCCCCTCACCGCGCAAAACATTGCAAATGAG
ATTTTTCCTTTTTCTTAGACCATTTCAAAAGTCATTGTTACTTAAGGGTG
GAGGTTGGAAGATTTCCAAAGAATAAAATATACAGAGAATATCTAACCAA
AGTTCCTAACACATACACAATTCAGAAAATGTAACTCACAGACAAGGGAT
AACAAGACCATTGACCCAATTTCAGAGCTTGACGTTTACAAAATGAACAC
AAGGCAGTGTGGGTTGTATGCGCGTTCTGTTCAGTTTCTCTCCTTTGGGG
TTGTTTGGGTCAGCCTGTTGTCTCATGAGACTGGGTGGGCTAAATTGAGC
AACATTTTGCTATAATAAGTCTGCAAGATTAGACCTTAGGCAACAAAAGC
CGGAAGGAGAAACTACATTTCCTATAAAATGTGGAACTGTGGGATAACAG
TGTAACAACACTATGACTACAAACAGGGAAATTTATATATGAGAAGGAAC
TGGATTGTATGTTACCTATATAAATGATCATGAGAAAGTCATGTTGTTCT
TTTGTTGTGATCTTTTAAACCAAATTTATAGTGCATTGAACCAAGTAATT
GTAGGCCATTATTTTAAAGTAGGTTGTAGCACAGCATGAATTAATAATCA
CACCAATTTTATTTTACTTCATTGGATTTATTTAGCAATTGTTttttagca
cttcctatatcccaggccctcttctacgcactttaaatgtattaacacat
ttcaattaatcctggcaacagcctgagaggtaggtactattactattccc
attttacagatggtggaactgaagcatggtgcaattaagtaagcagccaag
attcaaccggaattcaaaccaagcaatcaggctccacaacctgccttttt
aatcTGGCTCTCTGCCTTGTGCAAAAAGATGGTGAGttagtccgttctcg
cactgctataaagaaatatctgctgggcgcggtggctcacgcctgtaatc
ccaacactttgggaggccgaggcgggtggatcatgaggtcaggaattcaa
ggccagcctggccaagatggtgaaacccgtctctactaaaaatacaaaaa
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gaggcagagaattgcttgaacccgggaggcagaggtggcagtgagccgag
attgcgccactgcactccagcctgggtgacagagcaagactccatctcaa
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cccaggactttgggaggccgaggcgtgtggatcacgaggtcaggagttca
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gatcgcaccactgtactccagtctgggtgacagagcaagactctatctca
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aaaggagattggccaggcgcggtggctcatgcctgtaattccagcacttt
gggaggccgaggcgggtggatcacgaggtcaggagatggagaccatcctg
gctaaaatggtgaaaccccgtctctactaaaaaaaaatacaaaaaattac
ccgggtgtggtggcggttgcgtgtagtcccagctactccggaggctgagg
caggaaaatggcatgaacccgggaggcggagcttgcagtgagccaagatt
gcaccactgcagtccggcctgggcgaaagagcggaaatccgtctcaaaaa
aaaaaaaaagaaagaaaagaaaagaaaagaaaggaggtttaattggctca

FIG. 3.27

tggttctgcaggcttcacaggaatcctggtggcttctgcttctggggagg
cctcaggaagcttccaatcacggcggaaggcaaagggggtgcgaggtgtc
tcacatagtgggagcaagagcaagagagagctagagaggaggtgatgtac
acttttaaaaaacctaatctcacaagcactcactcactatcacgggaaca
gcaccaaaggaacagcaccaaggcgatgatgcgaaaccattcatgagaaa
tccgcccccatgatccaatcacctccccgccaggccccacctccaacact
ggggactacaattccacatggatttgatgggaacacacacccaagccatg
tcTGATGGACACATAGTTTATTTTctttgtgactctgcataggccattc
ttgccactgggaccccttccctcccaatcctcctggctttccctgcctgt
cagcaaactcctgctcctttttcaagcatcaactcggatttaccctctgc
tgtgatgtcttctgtgactcacatgcagatttaggcaccTGTTTATTGTG
TTCTCAATATATCTTACCCATACTATAGAAATATTTGTTGTTTTTTATCT
ACCTAGTGTTAAATTAAATAAGCACGAGGCCATTGGCCAGAGGCCCCTCtc
catattttgagtttctgtggaacaaacagcaacctaatagtatgtaaaca
aactgaaacctaatttaggagtatatttttgtaacatatagcctggtttc
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ccacgcccaataaggcagatgcctagctgttgccgatcaagtggtttctc
tacattgcttttgtgttcaccctagaaaagctcattgctcacactgccaa
gtggagttttctgaacctcttctggttctgagtgctgcctgattcatgaa
tcattctttgcccaaataaactctgttaaatttaatttgtctaaactgtt
tcttttaacaCTAGCTTCTATTCCGCCTTCTCTGACAAGCGTTCAGGAAC
CCACCCCACccccaccccgtactttgggtgtagcccatgtgatttaagtc
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caggttcatcgaactagagtgaatcctgggactgagcatgagcggctggg
aagaaacacacaagtttttgttgcaagtctggagctgctagcagacttca
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agaatgggaaagagtctgctggtgacattatttgatcctctgaatgatgc
ctcacttaaattcaagatatattcttggattttgtgcattaacaaattcc
ctttttgagcttaagcctgcttgatttatctatcatttgcaaccaaagga
acattaaccaataAATACATTTCACTGTATATCTGTGTCTATATATCTAT
ATGTATTTCATTTTACCAAGGTGTCTCCCTACTAACCATAATTCTTTGAG
GGCAGTAGATGCTCAATATTTGTCAAATGAATTCAGCTGAAGGGTGTTTT
GAAGGAGACTGACCTTAGAGGAGGGACATTTTAGGAAGGCTAATGGACTT
AGTGTGAGATGTGATCAAGGGACTCAACCAAGTTGAAGAGTAGGATTGAA
AGGGAAGGGACAAATACCAAAGAAAGATTTAACAAGGCAGTGATACAGAG
TGGGGTGGAGCAATAGTTAGATTAAAGCCTGAGTGCTACCCTGTTCTGCG
TATTTGTTTCTTTTGGTGTCTCTTTAGCAGCCAGCCTAAATTAAAAGTTT
ATTGTACTGGCTGATTATTGCCTGTCTAAATCACCCGTCTCTGTTAGTTT
ATCACAAGTGAAAAAATTAATGATAGAGAATCAGAGACTCACATATAAGC
AAATAAGCATGATTATTATAAGAAAGAGCTTTTATTAAACAATACTTTCA
GGTCTTCATAAGAATAGGGGTAGAATTTCAGAGACCCACATAACTCAGTG
TGCAGTAAATGCTGCTCCTGGGCAACTTAATGGAGCATAAACTGCCAGCA
ACGGTCCCAATTGAAATGGAGACTGGAAGGTGAAGTTGTCCTTCCTTTCT
GTAACCACCAGGCAAGAGGACACTTGTAAGGTGTGAGTAGCAGCACCCAA
AAACCAGCTGCAGGACTCAGTGGAAGGGAGGAATAAGGTCACTCTTAAAA
TCCTATCACCTCACATAGAAAAATAGCTAAGTCCTAATTAAGCTCAACAT
CGCCACTCTCAGCTTATCCCTGAGACAGGTCAGGAGAAGAGGGACCATTT
GCTTTGCTCTGGGATTGTTGCACTTCTGCAATCTGACTTTGtaaaaaaaa
aaaaaattaatttaaaCAGTTGCTACCATATGGGATAGTGTAGCTCGATG
GTTTCTTTCTCTCTCTCGTCCCTCTCCTGCTCTGCCTTCTATGTATTTAC
CACCCCTCTTGCAGAAATGCTCTCGTGGAATGTGGCtttttttttttttt
ttttgagatggactctcactcttgtcactcaggctggagtgcagtggcac
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tctcagcctctcaagtaactgggattacaggtgcccaccaccatgcccag
ctaattttttatatttttagtagagacagggtctcaccatgttggccaggc
tggtctcgaactcctgacctcacgtgatccacccacctcggccgcttaaa
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ttttttttttaagagatgggggtcttactctgttacccaagcagtggctt
gatcatagctccctgtagccttgaactcctgggctcaagcaatcctccca
cctcagcctccagaatagctgggattacatgtgtaagccactgcactcgg
ctaattctttagtgttttgtagagatgagggtcttgctctgttttggtct

FIG. 3.28

tgaattcctagggtctccctatgttgcccaggttggtctcaaatccctgg
gctcaagtgatcctaccacttcagcctcccaaagtgctgggattacaggt
gtaaaccactgtactggccAACTTCCTGTGTTTTAAAAATCCTCCCAGTT
GGGGCCAGTGCCCTAACCTAATGGATGCACAATGAGCCAGTTGAATGTGG
CCTCTTTTAGTCAAAAGGAAAGATTCTTTTTTTTTTTCCAAGTATTTCTT
TATTTATATTACTAGGCTTAAGTTACATGAAGAAAGACAACTAAGCAGTT
CTGCCCATTTCAGAAAAAGTTTCCAATCATCACCAATTATGTGACAACAA
ATAACTAGGAATGGTGACAGCTTTGGGTCAAGACCAACAAGGAAGAATGG
GCTCTGGTGCTACAGTTCATTTCCAACAAGAATATGGCACACCAGCCAGC
ACAGCCATGCTAACACTGGGCCTTCAGTGCCAAGCACAGATTCAGATCTA
TTCTCTGAAGTTAGCAAATCAAGTGAAATAACTGGAATTTTTTTTAAGTT
TAAAATGAAGCCCAAGTAAGTTTAAAACCATACTCTTGTCATATTTTCCT
TTCAAAATTCACATAAAACACACTTTTCATGCCAATAGCCCAGATATTTT
TTCTTACATAACCCACTATGTAGCTGCAGACAGACTCTTCTACCTCAAGA
TGTAAACACAGGGGAAAAAATTAATGGCCATCTGTCTAATATTCTCTCTA
TACACTGCTGTTGGATGGAAAATACAAAATTTTGTTTTAAAGGTTCCATC
TTAGATTCTCGCAACCTGCAGGTCATACATCTGACTCTGATGCTAAGGTG
ACAGTGAATGTCACCTGATGTTTGTTTTCAGTAAGGGGGATCTGGGAAGG
ATGAATTTATCTCTTTTTCTTCAAGAATTATCAGATGATACATGCTCCTC
AGAGCCTTCACTCTCTTGAACTTCAGCACTTTCCAGGATCACACAGCCTT
CCTTATAACATGGCTATCTCCAGTGGCAAATTCATAAATCCACCCCGGTT
TGCTATTGCAACTTTTGCAGCTCACATCTTGAACCCTGTGGCTGCCAGTG
AGCATGACCAGATCTTAAAGTTCACTGCACAGCAGGTTAACGACCTTGTT
AAAAGGCCAGGGCGCCTGTGAACTGAGTGGAGATGAGTTCTGGGCGGTTG
GTCAGGATCATGTCAGTTTGCACAGGAACACAGACAGGTACCACCGATAT
GATCAAGGAAAATTCTGCCCATTTTTATAGCTGAAGTTCTAAAATCTCTG
AGTGGCGATGAGATCCATGGCTGCCAGATCTCCTCGCCTGGGATGAAGGC
CCCAGGATTCTTGACAGTTAATTAAAACCAGAATTCATACTGAAGCAGGA
AATTTTCCCTGacccctcacaggagggggagtgcaggtgagtgggtgcag
gaattggggcgagtgctttggggcgctggcaggagcaaaactccatgagg
ccctgcagcacggtctagtggggtacccatgactcctgaagccccagaaa
gagtgttacagtgctcttttagcgttgccatctgtggacagcttaagtgt
taataactcagtggaaagtcagtgtgacagccttttgcactcgcacccaa
gttctcgttcgacatctaggaggaatgaggtcacacaacaaattggaggt
ggtatatgtgggggattttattgccagtgaaagtggctctctgcagaaag
gggagctgaaaaagggacagagcaggaaggtaatcttcccctgaagtcca
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cccagcactttgggaggcagagcaagagagagctaaggtggaggtgctgc
acacttttaagtcaagctgcttctcctctctgccggctgagttctggggt
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cggtattacgcttttcaccttgaggccggggccgtcgctggggacccacc
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AATGGTACACTGCCATTTCGCGTTATTCATTTTTTTAAAAATACATATCC
TTTAAGCTGGTTATTTACCTCTTTTTAAAAGGAAACTGTAAGGTCTTCCA
GGGCAGGGAGTATGTCTGTAAAGCCTtctagagctgggctccttgcttcc
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cttagtgtctcaatttcctcctctataaaacagagataatagtatttagc
ccagagggttgtggtgaagtgtgaatcatttctccatgtaaaacacatag
gacaggctgggcatggtggctcacgcctgtaatcccagcactttaggagg
cctaggcgggtggatcacctgaggtcaggagttcaagaccagcctgggca
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atggcgcacacctgtaatcccagttactcgggagactgaggcaggagaat
cacttgaacccgggagcggaggttgcggtgagccgagatcgtgccattgc
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ATAGGACAGAGCTCAGCACAGAGTAGACATTAAGGattatatcctttgct
tggcacaataccttgcacagggcaggcacgcaacagatgtctCTGgaatg
aaggaatgaatgagtgaatgaCTGGGTTAAGCATGTTGCCACCAGGTGGC
AGAAGAGCCTCACTATCAAGGCAGAACCCAAACACGAGACTCATGAGAAC
TCCCTCCTGAAGTCCAGATACACATTGAAAAAAAATAAAAAAAGCACTGA

FIG. 3.29

ACCCCATTTAGGCCTTGAAGTGAAGTTCCTCTTCTCTCTTGCCCTTCCTT
TCTCTCCCATCTCTGCTCACTCTCTGCTGTAATGAACCATTTCTTTCTTT
CCCACTTAATACAtattagtcagtttgggctgccacagcaaaatactaca
gactcagtagtttaaacaacagatatttaatgcatcacagttctggaggt
tggaagtccatgatcaaagtgccatacgggctggtttctggtgaggcttc
tcttcctggcttgtagctgtccaccttcccactgttattctcacagggcc
tcttctctgtgCCACACAGAGAGAGGAAGGAGAGGGAGTGGGAGATGGAG
AGATGTCAGATTCACACAATGAAGCCCTAACCGCCATTTTGACTGTATTT
GCAAATAGGGttttttttggtttgtttttgagacggagtcttgctctgtc
gcccaggctggagtgcagtcgtgcaatctcggctcactgcaacctccgcc
tcctgggttcacgccattgtcctgtctcagcctcccaagtagctgggact
gcaggcacccgccaccacactcagcaaattatttgtaatttagtagaga
tgggttttcaccatgttggtcaggctggtctcaaactcctgacctcgtga
tccgcccgccttggcctcccaaagtgctgggattgcaggtgtgagccact
gcaccGACCTGCAGATAGGGTTTTTAGGGAGggagagagagagggagatc
tggagcgtcttcttataaggacaccagtcctatgggattaggccccaccc
aagttacctcatttaatcttaattacctccctaaagaccctgtctccaag
tacagtcaaaccaggggttagggcttcattgtgtgaatctggaggggaca
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ACTTCCTACCAATGTGGTTTTTCATTCTTACTCTCTTGTTATTCCCACTC
TTCCCCCGACCCCCATCCGCCATCCCTCAATCTTTATATGGCTTTTCTAG
GGCTagttgtatttattgtaaactgaaaactccaggggggcaccattcatg
ccatagtcagcataggtttgcatatgtattatgacaatgttgaggctgat
ggcagcaacatgtcttgaggaaggggagtctttttctcattcacacaaag
gtgcTGGCCCCTTCGTTTTCCTCTGTTGTTTTCCTGTCCTCCTCCCCATC
ATTCTCTTTCTTCAGCCTTTCTCTCTCTTTCCTTACTCTCCTCTTCAGGC
TGAACCTGCTCCATGTCCGTAAAGAGATGATTTAATTCATCGCACCACAC
ATTCATCCAGTAATTTTGGTGGGCCAGGCCCTTTGTGGGTGCCAGATGGT
TCACCCTATTCTTGCACCTTTAAAGGAATCGGTCCATTTACACCCTAGAG
GTCAATACCCAATGGAATGTGCCTCCAACATCCTTGGATCATTCATGGTC
TTCATTTACCTTGGAGCAGACATTAAGACTCAAGCATTggccgggtgcgg
tggctcacgtctgtaataccagcactttgggaggccgatgtgggtggatc
acaaggtcaggagttcaagaccagcctggccaacatggtgaaaccccatc
tctactaaaaatacaaaaattagctgggcatggtggcacgtgcctgtaat
cccagctactcgagaggctgaggcaggagaattgcttgaactgggacctg
ggaggcggaggtagcagtgagctagatcgcgccattgcactccagcctgg
gctacagaatgagactctgtctcaaacacaaaaacaaacaaacaaaaaaC
AACAAAAAGACAAGACTCAAGCATGGAGGAGAAGAGAAGAGAATATAATC
Caataacataaactaatgtttattgaacacttgtgtgctgcacacagttc
tcatctctctctatgcatgacatttaatcatcaaaactgccttctcattt
tgtagatgagaaaactaagctgcagagaACgtggcagagactcctcctgg
tttcctaacttccattttcttttcctttatttaaataacaggagctcatg
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tcccttgcagtttgatgtggccatataactgcattctagacacctgaggt
gtgagtggaaatgatgtctgcaatttcagagttccatccttaaagggaag
ctgcttgcctctatgtcctcttttccttgtccccaggctgggacagggtt
aggggagtagtgaggcagctttgacaggagggtgaggacaggaagctggg
gaagagcagagcaaccactggaaggaAGcttcacactcactccccaccca
ctcactactcacccagagcaacttcccatcctgcaaactccaatcacggg
aagtatcctatagaggggtatccttttttaaagaaaaaaaaacctttgatac
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taccattgtgttgcaattacctacagtattcagtacagtaacgtgctgtt
caggtttgcagcctagagcaataggctacaccatatagcctaggtgtata
gtaggctataccatctaggtttgtgtaagtactgaacactccatgatgtt
tgcacaacggtcaaattgacaagtgacacatatcttggaacatatccctg
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GAAAGAAAACAGAAGGACCCATTGCCTTGAAGGAAGGAtggtagacggaa
taatgtccaccctggcctcccaaagacgtccaagtcctaattcctggaaa
tatgagtatgttactttacttggcaaacgggactttgcagatgtgcttca
agtcaggaagttgagatggggagattgtcctggatgatttgggtggaccc
catcaaatctcaggggctctctaagggaaagatgaaggtgggagcgtga

FIG. 3.30

gagccagataagacactgtgatgatggaagcagaggagagagagaagatg
ctacactgtgggccttaaagagagaagaaggggccctgatccgaagaatg
cagcttctagaagctggaaaaggcaaggaaatggaatctgccctagaacc
tcactaggaatgaatcgcagctgacaccttgcttttagctaagttaaacc
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agcaacgagccagcacctccctgaggcttgaagggcaacgggaaaggaaa
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aagtagtggccACAAAGGTGGGACTGTGGGTTGAACAGATCCCCAGAGGT
GTCTGTTATGCACAGTAAGCTCCAACAGTGAAAAATCATTTATAAAGggc
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gggcagattgcttaagcccaggagttccagaccagcctgggcaacatggc
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ggcacctgtagtcgcagctacttgggagggtgaggtaggcggatcacttg
aacctgggaggttgaagctgcagtgagctgtaatcatgccactgcactcc
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AAGGACTTTTGCCTCTAATAAAATATTCACAGTGGTTTCCTTACTTAATT
TCTGAGGTCAAACCAGAAAATATTAGCAGCTGACTTAATTCAAGAAGGAG
GAGCTTGAGTATACGTACTTGTTGGTGTGTCTTCAACTCTTGTTCTAGAT
TTTACTTTGTTTTAAATATGTAAAAATGCTTTTAGTGATTACAACTTATG
CTTCTTATTTCAACAGATATTTTAAAGGGAAAAATATATAATTGGATCAC
AGGATATAAAAAGAAATGCAGTTATCTATATGTGCAAAAGCCTAGCTAAT
TGATAAAAGCTATAAGTTGAGTCCTGCCACTCACCTTGGGGCAATGATTT
TTTATTTAtttattttattttattattattattttttagacagagttgc
ccaggctggagtgcagtggtgcgatctgggctcactgcaacctccacctc
ccgggttcaagcaattctctgcctcagcctcccaagtagctgggattaca
gggtgcaccaccacacccagctaattttgtatttatagtagacatggag
tttcaccatcttggccaggatggttccgaactcctgacctcgtgatccac
cactcggcctcccaaaatgctgggattacaagcataagccactgcaccac
gcccggccAATGACCCATTTTTTTCAGGCAAAGTAGCAATGGGAAAATAT
AAAGTTTCTCTAGTTTTAATATAGAAGTGGTTAACCTAATCACACAAGCC
ATACACAGGGTCATTTGGGAGAATGTGCAAGGAGGATTGCGTATTTTTAT
CTTTTCATAGTTTTCTTCTTGATAAATAAGCTTCTATTTTCAAGCCAAAT
CTCATCTTGCAATTTCCTGCCAACTTCACTTCTCTACAAAGTTTACCTTT
GCTTTTCCCATCTCTGCCCTCAGGCATTTAACAAACACTGTGCCTTTTCA
TTTTTCCAGATTTAAGTGAAACATTTTGCAGAAATGAGGAATGTGATAAC
AGCCCCTGAAGCCCTACCTGACAGCATGACATTAATTTGGGCCTGTTTTC
TCTCATACTTTTCAATTGCTCCCCAATTTATATTTAATTTGCCACAGGat
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AGCTAGAGGTTATCTAAGTGAAACTAGCTCGATTATCTAAAAAAAGTCAG
AATAAAATAATTATAAGCAAATTGGAAGAACAGCCAACGTTGTTACCAAT
AATTTCTTAGAGTTTGTTCAATTATTGTTTGTTATACTCTGTTTCCACTT
CTTTAGCCAAAATAAGCTCTAAGCAAATTCAAATCTATTTGTATAGATGA
AGTCTATGAATTTAACATGATAACTTGAAAAAATGTAAAACTTTggctgg
gtgtggtggctcacacctgtaatcccagcactgtgggaggctgtggcggg
cggatcacctaaggtcgggagctccagaccagcctggccaacattgtgaa
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cctgtaatcccagctactcaggaggctgaggcaggagaatcgcttgaacc
caggaggcggaggttgcagtgagccaagatcgtaccattgcattccagcc
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AAATAAATTCATGTGGATCTTACCCATATTTCCCATGATTTAGATAGGAG
TTGGTTTTAAGTTTATTTTTCCACTCAATGGGGGAAAGGATTTACTAGGA
AAATAATGTAAACAATCTATTTAAGAAGTCAAATGGCTTTTAAGCACTTA
AAAAGCTTTGATATTAGCAATTTACCCATAAATATTTTGTTAATTACATA
ATTTTTTTCTTTTTAGGAAATATTTCTTCTTTTCTTCTTCTTTTGGCTAA
GCCTCAGCAGCCAAAtttttattttactttattttagtttactttttag
agacagggcctccctctgtcacacacgctggagtgcagtggtatgatcat
agctcactataaccacaaactcctgggctcaagccatcctccctcctcag

FIG. 3.31

cctcccgagtaggtgggactacaggtgtgcaccactacacccagctaatt
tttgtagtttttgtagagacggggtcttgtcatgttacccaggctggcct
cgaactcctgggctcaagcaatcctccttcctcagcctcccaaaatgctg
ggattataggcgtgagccacagcaccAGCCTACCAGGTATGCTTTTAATA
CATATATATTGAATAAATAAACAAATTAAAGATCATCTGACAGAACCTTC
ACTGGATAATATTATTTTttcttttcctttttttaaaaaataaggcaggg
tctcaccgtgttgcccaggcttgtcttgaacttctgggctcaagtgatcc
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accagccTTCATTGGATAACATGTTATTTGACATTTCTTCTATCATTGTA
CATTGATGactgttggttgcctgcccagcagccattgcccccattactcc
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gagggcaggggtgcggctaaacattcttcaatgcacaggacagcccccac
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tctgcacactgggtggtactgctaatccagcttcaagcaagcacatgact
ccagagaatggcagagcaagacagaaagacttacatacattgggactgat
acatgaaaagaaaataaattgctttcttctttgaaccatcgtatttttta
gttttttttgtTTTAGCAGTTTAAGCTGTATGTATATGAGGTACTCCTGGG
GAAGGTTTTTTCCTCTGTGATcacacacacacatacacacacacacacac
acacacacacGGAGGGAATATTCATCTAAAggatgttgtaggatttgtgt
gagatggctggaaccatggctgctatcttgtgaccatgaggggaggtacc
tggtggttcaaaactgccctgctaagtgagaacggaataggaaggttgta
aacagcccaaatctttcttaaccttgttaagccattgagttgacgaactt
tgcatctgtcctgtctcaggacttcttgttaagcaagatggtatattttt
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TGATGGCTTTCAGACAGAAAATTAAAAATTTTAAAAAGTGCTATCCTAAC
TGATTCTCTCAATGTATTCAAGTGTAAAGAAATTACATGTCTAACCTCTC
ATGGAATTAGAGGGAAAAAATTTCATGTTATTTTAAGTATGTTCAGTTCT
TTTATTAACTCATATTGGTTTCCCCCCTACTCCTTACCCTTGCAACCAAG
ATAATTTGCATCTAAGAGGTTTTATTCTGTTTCCACTGATATGTTTAGAA
ATTACTATATCTGAGGTGGGTATATTGGGAAAACATACACTACCACTCCT
TTGCAGAAATGAGGGCTTATTGCAGCAGCTACTCGCCCTTGCAATGCTTC
CTGCTTGGAAACTCGAAGGACTACATTGAGCAGGTGGAATAAAGTTGAAT
CGAAGGTTCAACTTACAAGCAGTCAGGAGGAGGTCTGCCCTGAAGCACTG
TGCAGACTGGGACCTGCAGCAGGGCTGGGAGGGGGAGTGTCGAGGAAATG
CCTTTTGCATGTCAATGGAGCCCCGTTGCTGTTCTGTGCTGCACAGCCAC
ATGAGGTCATCCCAGATTAGAGGGTGCCCATGTCCAGGATCTTAAACCAA
TTACTTCCATCTCCATTGCTTCCTCTAAAGCCTCACTCTTAGTTCTACAC
AGTAATACTGCCTGGAAACTCCCCAAGGCCACCAAGCTCATACTAACAGG
TTTGTGATGTGGGCAAACTCCTTACATGATCTCAAAATGAAAGAAGAGGC
TGTTCACTGGAGGCAATAGCAAATCCCCTTTGTTCCTCTCTTGGCAGATG
AGGGCCTTCGCTCTCTCCCTAAGGGTTCCGCCTGTCACCATCTGTGCACC
CACTGTGGAAGGGCCAGCGCTAAGGTGAATTTCCATTTACTTCCTGCCAG
CAGATGGCTCCTCCTTTTGGTCTCATCTTGAATTGTTTGCCAGACCAGCC
AATTAGTCTCCTCACCCTTCCTGAAGCGTCCCAGGGAAGCAATATCATCA
CCAGCAGCCTATCATTATACCACGTCTTCTAAGCACCGTGATTCTAAATG

FIG. 3.32

CCTGCCGTGGAACAGAAGCTCATTCGCACATGGCTCTTTAACCCTTCCTT
GAAAGACCTCAATTCAACATTCTCTCTCTCGCTcacacacacacacacac
acacacaaatgcacactcacacacaGTACCTACAACCTGATCCAAGATAG
GAAACAAAATGACAGTATGCGGCATTCAATAATAAATTTAAAAATAAGAC
ATAATTTCAGACAGAATGCAGAAGGAAAAACACAGTAACTATATTTTCTG
ATCCCCACTGAGGACACaataaaaacttttttttaggccaggcacggtgg
ctcacgtgtgtaaccccagcactgtgggaggccgaggcgggcggatcacg
aggtcaggaggttgagaccatcctgactaacatggtgaaaccctgtctct
actaaaaatacaaaaattagcctgacgtagtggcgtgtgcctgtaatccc
agctacttgggaggctgaggcaggagaatctcttgaaccagggagttaga
ggttgaaatgagccgagatcgcaccactgcactccagcctggcgacagag
caagactccatcacaaaaaaaataatgatacaaaaaaattaattaaataa
ataaaaattaaaaataaaaaaaaGTGGAGGGtttttttttttttttttt
ttgacagagtcttgctctgtcgccaggctggagtgcagtggcgcaatctc
ggctcactgcaacctccaactctctggttcaagagattctcctgcctcag
cctcccgagtagctgggattacaggcacacactaccacgtcctgctaatt
tttgtatttttagtagagtcgggttttaccatgttggccaggctggtctt
gatctcctgacctcgtgatcctcccacctcagcctcctaaagttctggga
ttacgggaatgagccactgcatccggccAAAACTTTTTTTTTTTTTACCT
TGTGGATTTGTTCATATGAAAGAAATCTTTTAAGGATATAAAATCAAATT
GCACTGAGTTACATTTAACAAAGTATCTTTATCAGAAAAGAGTATATAGA
ATGACACTGGCAGGATTCTTCATCCCCGCAACCCAGGATGAATGATGACT
TTCCAGGCTAGGCCAAGGAGATTCTCCCAGCGCTATTCTTAGAAACATCA
ACAAGGCCCTTGTGCACTTGTTTTAGGGTTTTTCATCTTCAGACATTCCT
GCCTGATGCCTAAAGAAGACATATTATTCAGGGCATCCCATTTGAATACT
GTATCTGCTCTGATGCTTGAGCAAAGTGTCTGTAAAGCTAGACAGAGGGG
ACAACTGCTTCCATCCATGGGGCAAGGGAGCAATGATGAGATGATGGAGG
TTAAAGATATTTGTGAGGCAGACACAGCATCTGTGCAGAGGGGTAGAGGT
ATTTGTTTTTCCACTTTTCTGCTCTTGTTACCCTAACTTCCTTGTGTTCT
GTGATTATTGCACATGAGCTGGAGTAGCAGGGGAGGTTCAGTTCCTTTTG
GTGGTTGAGGTGGCAGGTAAGGAGGCATGGACACAGGACGAACCCCACTT
TTGGGCAACCGCCACCCTGAGGCAAGGGTGGGAAAAGCTCACTTTCCCAT
AAATAATCACTGGGCTGTTGTCCTTCAGTataagtgaatataagcaaagc
cccaagaacagtgcctggcacataAAATGCAGTAGCTCAGGGTGGGCTAT
AACCACTTGCATCTTctacagcagtgccttgtgccagcatgccctcaata
aacatttgttcagtgaaggaCTGTACAGCTCTGTGCCACCTGGCAGCTCC
AACTGTCCCAGTGGATCTTCCTCTTCCTTTGTTCTTTTCCTTGCAAACTT
TGCAATAAAGGGGGCATTGGCCCAACAGTTAACTCCCAAATCTTGAACAA
AGAGGATTACCCCTGCAACTCTGTTCCAAACTGGGAAGCTTCTGGCTTTG
TGGTGAGCTAGGGACTGCTGAAAACAACTAGAGATTAAAAGAAGCTGGAA
CCAGCTGGAGAATAAAGAAAACTGCTGCAAGCAAGTCACTGCAGGAAGTA
CCAGTGGTCTCCAAAAATGCAGTTGCACCAGATTTTACATACAATAAGGA
GGATTGGTCTCTCTAGACAGGAGAGAGTCAAGTGTTCCTCTGAGAAGGAA
CCAACTCCTGTAAATCAGGAAATCTCAGGCTCTCACTGGCCAAGGGGCAA
TGGGACACCTCCCCAAGGTGATTCATCGGCTCCCTCTGAACCCAGAAGCT
CAAGCCCATTGTGCTCCTTTTTGTAGACTCTTCTCTTACCCTAGTCCCCA
AGAATGTGCTCTGTGAGCAGGTTACACCCTTCACAAGACCCTTTCATGCC
CTGTGACTCCCTTCCCCATTGTTTGCATAGTCTGGCAGCTTCTGCCACTT
TCCCTGGTAAGCCCTGCCTTAAAGTGAACCCTCTTCTGTCAATCACCAGG
G

FIG. 3.33

>gi|4505028|ref|NM_000895.1| Homo sapiens leukotriene A4 hydrolase (LTA4H), mRNA
CTCTATCGACGAGTCTGGTAGCTGAGCGTTGGGCTGTAGGTCGCTGTGCTG
TGTGATCCCCCAGAGCCATGCCCGAGATAGTGGATACCTGTTCGTTGGCCT
CTCCGGCTTCCGTCTGCCGGACCAAGCACCTGCACCTGCGCTGCAGCGTC
GACTTTACTCGCCGGACGCTGACCGGGACTGCTGCTCTCACGGTCCAGTCT
CAGGAGGACAATCTGCGCAGCCTGGTTTTGGATACAAAGGACCTTACAAT
AGAAAAAGTAGTGATCAATGGACAAGAAGTCAAATATGCTCTTGGAGAA
AGACAAAGTTACAAGGGATCGCCAATGGAAATCTCTCTTCCTATCGCTTT
GAGCAAAAATCAAGAAATTGTTATAGAAATTTCTTTTGAGACCTCTCCAA
AATCTTCTGCTCTCCAGTGGCTCACTCCTGAACAGACTTCTGGGAAGGAAC
ACCCATATCTCTTTAGTCAGTGCCAGGCCATCCACTGCAGAGCAATCCTTC
CTTGTCAGGACACTCCTTCTGTGAAATTAACCTATACTGCAGAGGTGTCTG
TCCCTAAAGAACTGGTGGCACTTATGAGTGCTATTCGTGATGGAGAAACA
CCTGACCCAGAAGACCCAAGCAGGAAAATATACAAATTCATCCAAAAAG
TTCCAATACCCTGCTACCTGATTGCTTTAGTTGTTGGAGCTTTAGAAAGCA
GGCAAATTGGCCCAAGAACTTTGGTGTGGTCTGAGAAAGAGCAGGTGGA
AAAGTCTGCTTATGAGTTTTCTGAGACTGAATCTATGCTTAAAATAGCAGA
AGATCTGGGAGGACCGTATGTATGGGGACAGTATGACCTATTGGTCCTGC
CACCATCCTTCCCTTATGGTGGCATGGAGAATCCTTGCCTTACTTTTGTAA
CTCCTACTCTACTGGCAGGCGACAAGTCACTCTCCAATGTCATTGCACATG
AAATATCTCATAGCTGGACAGGGAATCTAGTGACCAACAAAACTTGGGAT
CACTTTTGGTTAAATGAGGGACATACTGTGTACTTGGAACGCCACATTTGC
GGACGATTGTTTGGTGAAAAGTTCAGACATTTTAATGCTCTGGGAGGATG
GGGAGAACTACAGAATTCGGTAAAGACATTTGGGGAGACACATCCTTTCA
CCAAACTTGTGGTTGATCTGACAGATATAGACCCTGATGTAGCTTATTCTT
CAGTTCCCTATGAGAAGGGCTTTGCTTTACTTTTTTACCTTGAACAACTGC
TTGGAGGACCAGAGATTTTCCTAGGATTCTTAAAAGCTTATGTTGAGAAGT
TTTCCTATAAGAGCATAACTACTGATGACTGGAAGGATTTCCTGTATTCCT
ATTTTAAAGATAAGGTTGATGTTCTCAATCAAGTTGATTGGAATGCCTGGC
TCTACTCTCCTGGACTGCCTCCCATAAAGCCCAATTATGATATGACTCTGA
CAAATGCTTGTATTGCCTTAAGTCAAAGATGGATTACTGCCAAAGAAGAT
GATTTAAATTCATTCAATGCCACAGACCTGAAGGATCTCTCTTCTCATCAA
TTGAATGAGTTTTTAGCACAGACGCTCCAGAGGGCACCTCTTCCATTGGG
GCACATAAAGCGAATGCAAGAGGTGTACAACTTCAATGCCATTAACAATT
CTGAAATACGATTCAGATGGCTGCGGCTCTGCATTCAATCCAAGTGGGAG
GACGCAATTCCTTTGGCGCTAAAGATGGCAACTGAACAAGGAAGAATGA
AGTTTACCCGGCCCTTATTCAAGGATCTTGCTGCCTTTGACAAATCCCATG
ATCAAGCTGTCCGAACCTACCAAGAGCACAAAGCAAGCATGCATCCCGTG
ACTGCAATGCTGGTGGGGAAAGACTTAAAAGTGGATTAAAGACCTGCGTA
TTGATGATTTAGAGATTTCTCTTTTTAAATGGAATTCGTAAAGAAATAT
AAAACTTCAGCTCACAATTAAAACTGTCTTTTTAGTTTTGGCTTTTTATTGT
TTTGTTGGTGATTTTACTGAAATAAAGATGAGCTACTTCTTC

FIG. 4

NP 000886
/translation="MPEIVDTCSLASPASVCRTKHLHLRCSVDFTRRTLTGTAALTVQS
QEDNLRSLVLDTKDLTIEKVVINGQEVKYALGERQSYKGSPMEISLPIALSKN
QEIVIEISFETSPKSSALQWLTPEQTSGKEHPYLFSQCQAIHCRAILPCQDTPSV
KLTYTAEVSVPKELVALMSAIRDGETPDPEDPSRKIYKFIQKVPIPCYLIALVV
GALESRQIGPRTLVWSEKEQVEKSAYEFSETESMLKIAEDLGGPYVWGQYDL
LVLPPSFPYGGMENPCLTFVTPTLLAGDKSLSNVIAHEISHSWTGNLVTNKTW
DHFWLNEGHTVYLERHICGRLFGEKFRHFNALGGWGELQNSVKTFGETHPFT
KLVVDLTDIDPDVAYSSVPYEKGFALLFYLEQLLGGPEIFLGFLKAYVEKFSY
KSITTDDWKDFLYSYFKDKVDVLNQVDWNAWLYSPGLPPIKPNYDMTLTNA
CIALSQRWITAKEDDLNSFNATDLKDLSSHQLNEFLAQTLQRAPLPLGHIKRM
QEVYNFNAINNSEIRFRWLRLCIQSKWEDAIPLALKMATEQGRMKFTRPLFK
DLAAFDKSHDQAVRTYQEHKASMHPVTAMLVGKDLKVD"

FIG. 5

LTA4H_3645 / SG12S16(Y=C/T)
CACTCCAGCCTGGGCGACAGAGTGAGACCCTGTCTCAAAACAAAACAAAACAAAAAC
TGCTAGGGAGAGTGAGAGCCAGGGAAAAGTCAGGATTCCGGGAATAGGCAGGAATAT
GTCTCTTCCATACCTGTCCCACCTTGGGTGTTCACTCCTATTGTAACTTTAGTCACTGCA
TTAGCACTTTGAGGGGTTATTTGGTCAGGACACCGCTCCCCACCCCCACCCCATGCCAA
CAATTATACTCTAAGACACCATTCCTCTTACACAATTTATTTGACCAGAGGTGGACCCA
ACCTGGGTTAGAGTCTCACCTCTGGGAATTTGGAATTGTGATAGCCTCCCCATGTGGTC
AGAGCTATTTGTAACAGTAAAGCTGGAGAGTGGCCGGCCTGTACAACGTGGACTAGA
GAGGCAGAGGTGAGGGACAGGAGCACTGACGGTGCTGCAGTCCTGGGCATCAGACCC
CTTCTGTC
[Y]
GTCCCAGGTTCTGATAATCTCCCCATACCTAGCATCCTTAAAATAATCTTCCTTTTCCCT
TTTTGACTTCTGGTCACTTGGATTGCTGTTACTTGCAATCAAAGAATTCTAACACAGCT
ATGGTTCTAATTAATTCTAACTAATAGAGCTAATACACTAATAATTCTACCTAGTACAG
CTATGTGTGCTGAGATGCCCTGGGGCACTACGTTGCATTGGCAGGGGTGCTTTGTTATG
TTTGTCTTTTATTTGGTTCAAGTTATTTTGTTGTCTTTGAACAGACTGTGAGAGGGATGG
GAAAGACTGGTGCTTGGGGTGGCCATCTGACCCCTGATGGACAGGAGACCAGGACAA
GCCCACTGGATGAGCCGGAGGGGTCCAGGAGGAGGGAGTTGAGAGCTCCTGCTAGGG
TTGACACATTCTGGTAAGGAGTTCATCTGCTGTCCACCAGGTAGGTGGTGTGCAAATA
CAACTAAGCATTCATGTTTAA

LTA4H_3705 (K=G/T)
ACTGCTAGGGAGAGTGAGAGCCAGGGAAAAGTCAGGATTCCGGGAATAGGCAGGAAT
ATGTCTCTTCCATACCTGTCCCACCTTGGGTGTTCACTCCTATTGTAACTTTAGTCACTG
CATTAGCACTTTGAGGGGTTATTTGGTCAGGACACCGCTCCCCACCCCCACCCCATGCC
AACAATTATACTCTAAGACACCATTCCTCTTACACAATTTATTTGACCAGAGGTGGACC
CAACCTGGGTTAGAGTCTCACCTCTGGGAATTTGGAATTGTGATAGCCTCCCCATGTGG
TCAGAGCTATTTGTAACAGTAAAGCTGGAGAGTGGCCGGCCTGTACAACGTGGACTAG
AGAGGCAGAGGTGAGGGACAGGAGCACTGACGGTGCTGCAGTCCTGGGCATCAGACC
CCTTCTGTCCGTCCCAGGTTCTGATAATCTCCCCATACCTAGCATCCTTAAAATAATCT
TCCTTTTCCC
[K]
TTTTGACTTCTGGTCACTTGGATTGCTGTTACTTGCAATCAAAGAATTCTAACACAGCT
ATGGTTCTAATTAATTCTAACTAATAGAGCTAATACACTAATAATTCTACCTAGTACAG
CTATGTGTGCTGAGATGCCCTGGGGCACTACGTTGCATTGGCAGGGGTGCTTTGTTATG
TTTGTCTTTTATTTGGTTCAAGTTATTTTGTTGTCTTTGAACAGACTGTGAGAGGGATGG
GAAAGACTGGTGCTTGGGGTGGCCATCTGACCCCTGATGGACAGGAGACCAGGACAA
GCCCACTGGATGAGCCGGAGGGGTCCAGGAGGAGGGAGTTGAGAGCTCCTGCTAGGG
TTGACACATTCTGGTAAGGAGTTCATCTGCTGTCCACCAGGTAGGTGGTGTGCAAATA
CAACTAAGCATTCATGTTTAAGGTTTTTTTTTAATTTTTTATTTTTCGAGGCAGAGTCTC
CATTGCCCAGGCTGGAGTGCAATGGCGCCAT

LTA4H_3929 (Y=C/T)
ATTTATTTGACCAGAGGTGGACCCAACCTGGGTTAGAGTCTCACCTCTGGGAATTTGG
AATTGTGATAGCCTCCCCATGTGGTCAGAGCTATTTGTAACAGTAAAGCTGGAGAGTG
GCCGGCCTGTACAACGTGGACTAGAGAGGCAGAGGTGAGGGACAGGAGCACTGACGG
TGCTGCAGTCCTGGGCATCAGACCCCTTCTGTCCGTCCCAGGTTCTGATAATCTCCCCA
TACCTAGCATCCTTAAAATAATCTTCCTTTTCCCTTTTTGACTTCTGGTCACTTGGATTG
CTGTTACTTGCAATCAAAGAATTCTAACACAGCTATGGTTCTAATTAATTCTAACTAAT
AGAGCTAATACACTAATAATTCTACCTAGTACAGCTATGTGTGCTGAGATGCCCTGGG
GCACTACGTTGCATTGGCAGGGGTGCTTTGTTATGTTTGTCTTTTATTTGGTTCAAGTTA
TTTTGTTGTCTTTGAACAGAC
[Y]
GTGAGAGGGATGGGAAAGACTGGTGCTTGGGGTGGCCATCTGACCCCTGATGGACAG
GAGACCAGGACAAGCCCACTGGATGAGCCGGAGGGGTCCAGGAGGAGGGAGTTGAG
AGCTCCTGCTAGGGTTGACACATTCTGGTAAGGAGTTCATCTGCTGTCCACCAGGTAG
GTGGTGTGCAAATACAACTAAGCATTCATGTTTAAGGTTTTTTTTTAATTTTTTATTTTT
CGAGGCAGAGTCTCCATTGCCCAGGCTGGAGTGCAATGGCGCCATCTCGGCTCACTAC
AACCCCTGCCTCCCAGATTAAAGTGCTTATCCTCCCTCAGCCTCCTGAGTAGCTGGAAT

FIG. 6.1

TACAGTCGTGCCTCCACGCCCAGCTAATTTTTGTATTTTTAGTAGAGACGGGGTTTCAC
CATGTTGGCCAGGCTGGTCTCAAACTCCTGACCTCAGGTGATTCACCCGCCTTGGCCTC
CCAAAGTGCTGGGATTACAGGCATGAACCACTGC

LTA4H_3941 (S=C/G)
GAGGTGGACCCAACCTGGGTTAGAGTCTCACCTCTGGGAATTTGGAATTGTGATAGCC
TCCCCATGTGGTCAGAGCTATTTGTAACAGTAAAGCTGGAGAGTGGCCGGCCTGTACA
ACGTGGACTAGAGAGGCAGAGGTGAGGGACAGGAGCACTGACGGTGCTGCAGTCCTG
GGCATCAGACCCCTTCTGTCCGTCCCAGGTTCTGATAATCTCCCCATACCTAGCATCCT
TAAAATAATCTTCCTTTTCCCTTTTTGACTTCTGGTCACTTGGATTGCTGTTACTTGCAA
TCAAAGAATTCTAACACAGCTATGGTTCTAATTAATTCTAACTAATAGAGCTAATACA
CTAATAATTCTACCTAGTACAGCTATGTGTGCTGAGATGCCCTGGGGCACTACGTTGCA
TTGGCAGGGGTGCTTTGTTATGTTTGTCTTTTATTTGGTTCAAGTTATTTTGTTGTCTTT
GAACAGACTGTGAGAGGGAT
[S]
GGAAAGACTGGTGCTTGGGGTGGCCATCTGACCCCTGATGGACAGGAGACCAGGACA
AGCCCACTGGATGAGCCGGAGGGGTCCAGGAGGAGGGAGTTGAGAGCTCCTGCTAGG
GTTGACACATTCTGGTAAGGAGTTCATCTGCTGTCCACCAGGTAGGTGGTGTGCAAAT
ACAACTAAGCATTCATGTTTAAGGTTTTTTTTTAATTTTTTATTTTTCGAGGCAGAGTCT
CCATTGCCCAGGCTGGAGTGCAATGGCGCCATCTCGGCTCACTACAACCCCTGCCTCC
CAGATTAAAGTGCTTATCCTCCCTCAGCCTCCTGAGTAGCTGGAATTACAGTCGTGCCT
CCACGCCCAGCTAATTTTTGTATTTTTAGTAGAGACGGGGTTTCACCATGTTGGCCAGG
CTGGTCTCAAACTCCTGACCTCAGGTGATTCACCCGCCTTGGCCTCCCAAAGTGCTGGG
ATTACAGGCATGAACCACTGCGCCCGGACTTAT

LTA4H_3983 (W=A/T)
TGGAATTGTGATAGCCTCCCCATGTGGTCAGAGCTATTTGTAACAGTAAAGCTGGAGA
GTGGCCGGCCTGTACAACGTGGACTAGAGAGGCAGAGGTGAGGGACAGGAGCACTGA
CGGTGCTGCAGTCCTGGGCATCAGACCCCTTCTGTCCGTCCCAGGTTCTGATAATCTCC
CCATACCTAGCATCCTTAAAATAATCTTCCTTTTCCCTTTTTGACTTCTGGTCACTTGGA
TTGCTGTTACTTGCAATCAAAGAATTCTAACACAGCTATGGTTCTAATTAATTCTAACT
AATAGAGCTAATACACTAATAATTCTACCTAGTACAGCTATGTGTGCTGAGATGCCCT
GGGGCACTACGTTGCATTGGCAGGGGTGCTTTGTTATGTTTGTCTTTTATTTGGTTCAA
GTTATTTTGTTGTCTTTGAACAGACTGTGAGAGGGATGGGAAAGACTGGTGCTTGGGG
TGGCCATCTGACCCCTGATGG
[W]
CAGGAGACCAGGACAAGCCCACTGGATGAGCCGGAGGGGTCCAGGAGGAGGGAGTTG
AGAGCTCCTGCTAGGGTTGACACATTCTGGTAAGGAGTTCATCTGCTGTCCACCAGGT
AGGTGGTGTGCAAATACAACTAAGCATTCATGTTTAAGGTTTTTTTTTAATTTTTTATTT
TTCGAGGCAGAGTCTCCATTGCCCAGGCTGGAGTGCAATGGCGCCATCTCGGCTCACT
ACAACCCCTGCCTCCCAGATTAAAGTGCTTATCCTCCCTCAGCCTCCTGAGTAGCTGGA
ATTACAGTCGTGCCTCCACGCCCAGCTAATTTTTGTATTTTTAGTAGAGACGGGGTTTC
ACCATGTTGGCCAGGCTGGTCTCAAACTCCTGACCTCAGGTGATTCACCCGCCTTGGCC
TCCCAAAGTGCTGGGATTACAGGCATGAACCACTGCGCCCGGACTTATGTTTAAGGTT
ATTTAAAAAGCAAAGCAAAATCCTAACCATGT

LTA4H_4295 (R=A/G)
TACCTAGTACAGCTATGTGTGCTGAGATGCCCTGGGGCACTACGTTGCATTGGCAGGG
GTGCTTTGTTATGTTTGTCTTTTATTTGGTTCAAGTTATTTTGTTGTCTTTGAACAGACT
GTGAGAGGGATGGGAAAGACTGGTGCTTGGGGTGGCCATCTGACCCCTGATGGACAG
GAGACCAGGACAAGCCCACTGGATGAGCCGGAGGGGTCCAGGAGGAGGGAGTTGAG
AGCTCCTGCTAGGGTTGACACATTCTGGTAAGGAGTTCATCTGCTGTCCACCAGGTAG
GTGGTGTGCAAATACAACTAAGCATTCATGTTTAAGGTTTTTTTTTAATTTTTTATTTTT
CGAGGCAGAGTCTCCATTGCCCAGGCTGGAGTGCAATGGCGCCATCTCGGCTCACTAC
AACCCCTGCCTCCCAGATTAAAGTGCTTATCCTCCCTCAGCCTCCTGAGTAGCTGGAAT
TACAGTCGTGCCTCCAC
[R]
CCCAGCTAATTTTTGTATTTTTAGTAGAGACGGGGTTTCACCATGTTGGCCAGGCTGGT
CTCAAACTCCTGACCTCAGGTGATTCACCCGCCTTGGCCTCCCAAAGTGCTGGGATTAC

FIG. 6.2

AGGCATGAACCACTGCGCCCGGACTTATGTTTAAGGTTATTTAAAAAGCAAAGCAAAA
TCCTAACCATGTTGAATTTTTGAATCTGCAGCAGATTCAAATTAATGAATTTAAATCAT
ATATCAGGTAAAATACTACCTTGACATATTTTGTGATCATACTGAGAGAAAATTAATA
TAAAGCTAATTCAAAATTTTTTAATTTGTAAATCAAAAGATTAAACCTTGTTAAAATTT
ACAAAGAATATGCCACTATAAGAAGAAGTAGCTCAACTTTATTTCAGTAAAATCACCA
ACAAAACAATAAAAAGCCAAAACTAAAAAGACAGTTTTAATTGTGAGCTGAAGTTTTA
TATTTCTTTACGAATTCCATTTAAAAAAGAGA

LTA4H_4376 (R=A/G)
TTTGGTTCAAGTTATTTTGTTGTCTTTGAACAGACTGTGAGAGGGATGGGAAAGACTG
GTGCTTGGGGTGGCCATCTGACCCCTGATGGACAGGAGACCAGGACAAGCCCACTGG
ATGAGCCGGAGGGGTCCAGGAGGAGGGAGTTGAGAGCTCCTGCTAGGGTTGACACAT
TCTGGTAAGGAGTTCATCTGCTGTCCACCAGGTAGGTGGTGTGCAAATACAACTAAGC
ATTCATGTTTAAGGTTTTTTTTTAATTTTTTATTTTTCGAGGCAGAGTCTCCATTGCCCA
GGCTGGAGTGCAATGGCGCCATCTCGGCTCACTACAACCCCTGCCTCCCAGATTAAAG
TGCTTATCCTCCCTCAGCCTCCTGAGTAGCTGGAATTACAGTCGTGCCTCCACGCCCAG
CTAATTTTTGTATTTTTAGTAGAGACGGGGTTTCACCATGTTGGCCAGGCTGGTCTCAA
ACTCCTGACCTCAGGT
[R]
ATTCACCCGCCTTGGCCTCCCAAAGTGCTGGGATTACAGGCATGAACCACTGCGCCCG
GACTTATGTTTAAGGTTATTTAAAAAGCAAAGCAAAATCCTAACCATGTTGAATTTTTG
AATCTGCAGCAGATTCAAATTAATGAATTTAAATCATATATCAGGTAAAATACTACCT
TGACATATTTTGTGATCATACTGAGAGAAAATTAATATAAAGCTAATTCAAAATTTTTT
AATTTGTAAATCAAAAGATTAAACCTTGTTAAAATTTACAAAGAATATGCCACTATAA
GAAGAAGTAGCTCAACTTTATTTCAGTAAAATCACCAACAAAACAATAAAAAGCCAA
AACTAAAAAGACAGTTTTAATTGTGAGCTGAAGTTTTATATTTCTTTACGAATTCCATT
TAAAAAAGAGAAATCTCTAAAATCATCAATACGCAGGTCTTTAATCCACTTTTAAGTC
TTTCCCCACCAGCATTGCAGTCACGGGAT

LTA4H_4422 (R=A/G)
GAAAGACTGGTGCTTGGGGTGGCCATCTGACCCCTGATGGACAGGAGACCAGGACAA
GCCCACTGGATGAGCCGGAGGGGTCCAGGAGGAGGGAGTTGAGAGCTCCTGCTAGGG
TTGACACATTCTGGTAAGGAGTTCATCTGCTGTCCACCAGGTAGGTGGTGTGCAAATA
CAACTAAGCATTCATGTTTAAGGTTTTTTTTTAATTTTTTATTTTTCGAGGCAGAGTCTC
CATTGCCCAGGCTGGAGTGCAATGGCGCCATCTCGGCTCACTACAACCCCTGCCTCCC
AGATTAAAGTGCTTATCCTCCCTCAGCCTCCTGAGTAGCTGGAATTACAGTCGTGCCTC
CACGCCCAGCTAATTTTTGTATTTTTAGTAGAGACGGGGTTTCACCATGTTGGCCAGGC
TGGTCTCAAACTCCTGACCTCAGGTGATTCACCCGCCTTGGCCTCCCAAAGTGCTGGGA
TTACAGGCATGA
[R]
CCACTGCGCCCGGACTTATGTTTAAGGTTATTTAAAAAGCAAAGCAAAATCCTAACCA
TGTTGAATTTTTGAATCTGCAGCAGATTCAAATTAATGAATTTAAATCATATATCAGGT
AAAATACTACCTTGACATATTTTGTGATCATACTGAGAGAAAATTAATATAAAGCTAA
TTCAAAATTTTTTAATTTGTAAATCAAAAGATTAAACCTTGTTAAAATTTACAAAGAAT
ATGCCACTATAAGAAGAAGTAGCTCAACTTTATTTCAGTAAAATCACCAACAAAACAA
TAAAAAGCCAAAACTAAAAAGACAGTTTTAATTGTGAGCTGAAGTTTTATATTTCTTTA
CGAATTCCATTTAAAAAAGAGAAATCTCTAAAATCATCAATACGCAGGTCTTTAATCC
ACTTTTAAGTCTTTCCCCACCAGCATTGCAGTCACGGGATGCATGCTTGCTTTGTGCTC
TTGGTAGGTTCGGACAGCTTGATCATGGGA

LTA4H_4487 (W=A/T)
ACTGGATGAGCCGGAGGGGTCCAGGAGGAGGGAGTTGAGAGCTCCTGCTAGGGTTGA
CACATTCTGGTAAGGAGTTCATCTGCTGTCCACCAGGTAGGTGGTGTGCAAATACAAC
TAAGCATTCATGTTTAAGGTTTTTTTTTAATTTTTTATTTTTCGAGGCAGAGTCTCCATT
GCCCAGGCTGGAGTGCAATGGCGCCATCTCGGCTCACTACAACCCCTGCCTCCCAGAT
TAAAGTGCTTATCCTCCCTCAGCCTCCTGAGTAGCTGGAATTACAGTCGTGCCTCCACG
CCCAGCTAATTTTTGTATTTTTAGTAGAGACGGGGTTTCACCATGTTGGCCAGGCTGGT
CTCAAACTCCTGACCTCAGGTGATTCACCCGCCTTGGCCTCCCAAAGTGCTGGGATTAC

FIG. 6.3

AGGCATGAACCACTGCGCCCGGACTTATGTTTAAGGTTATTTAAAAAGCAAAGCAAAA
TCCTAACCATGTTGA
[W]
TTTTTGAATCTGCAGCAGATTCAAATTAATGAATTTAAATCATATATCAGGTAAAATAC
TACCTTGACATATTTTGTGATCATACTGAGAGAAAATTAATATAAAGCTAATTCAAAA
TTTTTTAATTTGTAAATCAAAAGATTAAACCTTGTTAAAATTTACAAAGAATATGCCAC
TATAAGAAGAAGTAGCTCAACTTTATTTCAGTAAAATCACCAACAAAACAATAAAAAG
CCAAAACTAAAAAGACAGTTTTAATTGTGAGCTGAAGTTTTATATTTCTTTACGAATTC
CATTTAAAAAAGAGAAATCTCTAAAATCATCAATACGCAGGTCTTTAATCCACTTTTA
AGTCTTTCCCCACCAGCATTGCAGTCACGGGATGCATGCTTGCTTTGTGCTCTTGGTAG
GTTCGGACAGCTTGATCATGGGATTTGTCAAAGGCAGCAAGATCCCTGCCAAAAAAGA
AAAAATTGAAAAGAAAGAAAGGCGA

LTA4H_4575 / SG12S17 (R=A/G)
CTGTCCACCAGGTAGGTGGTGTGCAAATACAACTAAGCATTCATGTTTAAGGTTTTTTT
TTAATTTTTTATTTTTCGAGGCAGAGTCTCCATTGCCCAGGCTGGAGTGCAATGGCGCC
ATCTCGGCTCACTACAACCCCTGCCTCCCAGATTAAAGTGCTTATCCTCCCTCAGCCTC
CTGAGTAGCTGGAATTACAGTCGTGCCTCCACGCCCAGCTAATTTTTGTATTTTTAGTA
GAGACGGGGTTTCACCATGTTGGCCAGGCTGGTCTCAAACTCCTGACCTCAGGTGATT
CACCCGCCTTGGCCTCCCAAAGTGCTGGGATTACAGGCATGAACCACTGCGCCCGGAC
TTATGTTTAAGGTTATTTAAAAAGCAAAGCAAAATCCTAACCATGTTGAATTTTTGAAT
CTGCAGCAGATTCAAATTAATGAATTTAAATCATATATCAGGTAAAATACTACCTTGA
CATATTTTGTGATCATACTG
[R]
GAGAAAATTAATATAAAGCTAATTCAAAATTTTTTAATTTGTAAATCAAAAGATTAAA
CCTTGTTAAAATTTACAAAGAATATGCCACTATAAGAAGAAGTAGCTCAACTTTATTTC
AGTAAAATCACCAACAAAACAATAAAAAGCCAAAACTAAAAAGACAGTTTTAATTGT
GAGCTGAAGTTTTATATTTCTTTACGAATTCCATTTAAAAAAGAGAAATCTCTAAAATC
ATCAATACGCAGGTCTTTAATCCACTTTTAAGTCTTTCCCCACCAGCATTGCAGTCACG
GGATGCATGCTTGCTTTGTGCTCTTGGTAGGTTCGGACAGCTTGATCATGGGATTTGTC
AAAGGCAGCAAGATCCCTGCCAAAAAAGAAAAAATTGAAAAGAAAGAAAGGCGAGA
AGGAGACAGAGGAGGAGAAAGGGAGGGAGAGAAGAAAGAAAGGAGGGAAGGGGTT
CAGAGGAAAGGAAAAAGGAAGGAGAAAGAGAATAAGAA

LTA4H_5435 (Y=C/T)
CAAGATCCCTGCCAAAAAAGAAAAAATTGAAAAGAAAGAAAGGCGAGAAGGAGACA
GAGGAGGAGAAAGGGAGGGAGAGAAGAAAGAAAGGAGGGAAGGGGTTCAGAGGAA
AGGAAAAAGGAAGGAGAAAGAGAATAAGAACACAAGTCAATACCCAAGATTAAATT
AAAGGATGTCAGCAGGGGTGACAGCCAGCATCACCCAAATAAGGCACCAGTCCCAGC
CAATCAGATGGGTATGGTCCTGCCACAGGGTCCCAGAGACCTCCTTCTGTACCAGAGA
CTGGCCTTTATACTGGCAGATCAGACATTTTGCAGCAAGTTACAGGGAAGGGCTAGAG
TGGCTGGGACCCGTGGCTATTTACCAAGCAGCATGGAAGGATTTTATTATTTGAACAG
AGTCCTCTCATCTCCTGGCTAAATATCAGCCCTGTATGTGAGAGTGAGCCTCAAAGCCT
TTCTTTTTAAAAACTGCTTTTAAAAAAAATTTTTTAATCAAGA
[Y]
TTTAAGAGTATGAAAACACTAAAATTTATATAGAATTTCTGAAAACTTCAAATAATTG
AGAATAAAAGTCCTGACCACAGTGAAATAATAAATACATAATAAATAATACACGAAA
TAAATAATAAATACACTAAATAAAAAGGACCTACCATACAAAAGGTAGGATTAGTCA
TTTTTAATGTAACTACTATAAACATCATAAAACAGAAATACTTATTTTTCCCACAAAAG
GTATACTCTTATTTATTTTATTCATTTTTTTTTTTTGAGACAGAGTCTCGCACTGTCACC
CGGGCTGGAGGAGCTGGAGAGCAATGGCGCAATCTCAGCTCACTGCAACCTCTGCCTC
CCGGGTTCAAGCGATTCTCCTGCCTCAGCCTCCCAAGTAGCTAGGATTACAGGTGCCT
ACCACCACACCTGGCTAATTTTTTGTATTTTTAGTACAGACAGGGTTTCACTATGTTAG
CCAGGCTGGTCTCAAACTCCTGACCT

LTA4H_6468 (Y=C/T)
CAGGCGTGAGCCACCGCGCCCGGCCCAAGTATACTCTTATTTAAAAACCTATTTAAAG
TATACTTTACTCAATTCAAAGCTAGATGGGTTTTAATTAGGGAAAGCATATAAAATAT
ACTTAAAACTTAATTTTGTGGTCACATCAAAAAAGAGATAATGACTTATTTTGCCAAGT

FIG. 6.4

TTTATGATATTATATGGCCATCACTTTTGATGGCCAAAACTGCAATTACTTTTGCACCC
ACCTAAATACTTGTGAAGTAAATGAAAAGCAAACAAAAGTAATCATGGATATTTATGG
CATGATTTTTTTTTCCAGAATTTGGACAAAATTCATAAAGACCTTGACTGAGATATTCT
TGTATCTTGCTGTCAAGATACAACTTATCCCCCTCTCACTAAGCATTCCTTTATTATGTC
AAGCAACCTACCCTTGACCTCTATGCAACATTTGAACACAAAAGAGTTAGCTTTATCT
GCTTATTTCTCCTTACATTTAACTTCAGACT
[Y]
TCTTTCTTGTCTATACCTACCCACCAATTATCTTCTAGTTACCTTTAAAAATCTTTGTGT
ATATAAGGCTATCTTTGATTTATTTCTATTTTATCAGTATCTAACTCTATTTGATCCAAA
ATAGTAATCCATATATAATGCTTCTAAAAAGAGGAATGAAATTATTTCACATTTTAAAT
ATTTATAAGTGTGAATCCCTATTCCAAAATTATACTGATAAACTTTAACAAATTAAAAA
ATATTGTCATATAGATTACGTTTAAATATTTGACAGTTTTCTTCCTGTTTCTTAGATGAA
TTCAAAGTACGGTCTGAGTGGGTTCTTACTTGAATAAGGGCCGGGTAAACTTCATTCTT
CCTTGTTCAGTTGCCATCTTTAGCGCCAAAGGAATTGCGTCCTCCCACTTGGATTGAAT
GCAGAGCCGCAGCCATCTAAAAGGAGGATTTGGGGGGAGCATGGAGTAGAAAATGAG
GAAGGGGCAGGATATGACAGGTATATC

LTA4H_6647 (Y=C/T)
TGATATTATATGGCCATCACTTTTGATGGCCAAAACTGCAATTACTTTTGCACCCACCT
AAATACTTGTGAAGTAAATGAAAAGCAAACAAAAGTAATCATGGATATTTATGGCATG
ATTTTTTTTTCCAGAATTTGGACAAAATTCATAAAGACCTTGACTGAGATATTCTTGTA
TCTTGCTGTCAAGATACAACTTATCCCCCTCTCACTAAGCATTCCTTTATTATGTCAAG
CAACCTACCCTTGACCTCTATGCAACATTTGAACACAAAAGAGTTAGCTTTATCTGCTT
ATTTCTCCTTACATTTAACTTCAGACTCTCTTTCTTGTCTATACCTACCCACCAATTATC
TTCTAGTTACCTTTAAAAATCTTTGTGTATATAAGGCTATCTTTGATTTATTTCTATTTT
ATCAGTATCTAACTCTATTTGATCCAAAATAGTAATCCATATATAATGCTTCTAAAAAG
AGGAATGAAATTATTTCACATTTTAAA
[Y]
ATTTATAAGTGTGAATCCCTATTCCAAAATTATACTGATAAACTTTAACAAATTAAAAA
ATATTGTCATATAGATTACGTTTAAATATTTGACAGTTTTCTTCCTGTTTCTTAGATGAA
TTCAAAGTACGGTCTGAGTGGGTTCTTACTTGAATAAGGGCCGGGTAAACTTCATTCTT
CCTTGTTCAGTTGCCATCTTTAGCGCCAAAGGAATTGCGTCCTCCCACTTGGATTGAAT
GCAGAGCCGCAGCCATCTAAAAGGAGGATTTGGGGGGAGCATGGAGTAGAAAATGAG
GAAGGGGCAGGATATGACAGGTATATCTTAATATTACTTCTGTAGTGATATGAATAAC
CCCACTATAGTTATACTGTACACCACTTTATGGTATGTCTTGATTCTGAGACTCTCAAA
TCCTTATATATACAATTTAATAATTGGTGAAGAGAAAGAAGAGGAGCTGGTTCTTGAA
AAAGATCATATATTTTTAAAGGTCTGGATCA

LTA4H_7139 / SG12S18 (W=A/T)
AAATATTTATAAGTGTGAATCCCTATTCCAAAATTATACTGATAAACTTTAACAAATTA
AAAAATATTGTCATATAGATTACGTTTAAATATTTGACAGTTTTCTTCCTGTTTCTTAGA
TGAATTCAAAGTACGGTCTGAGTGGGTTCTTACTTGAATAAGGGCCGGGTAAACTTCA
TTCTTCCTTGTTCAGTTGCCATCTTTAGCGCCAAAGGAATTGCGTCCTCCCACTTGGATT
GAATGCAGAGCCGCAGCCATCTAAAAGGAGGATTTGGGGGGAGCATGGAGTAGAAAA
TGAGGAAGGGGCAGGATATGACAGGTATATCTTAATATTACTTCTGTAGTGATATGAA
TAACCCCACTATAGTTATACTGTACACCACTTTATGGTATGTCTTGATTCTGAGACTCT
CAAATCCTTATATATACAATTTAATAATTGGTGAAGAGAAAGAAGAGGAGCTGGTTCT
TGAAAAAGATCATATATTTTTAAAGG
[W]
CTGGATCAGGTAGGTGCTCACATACCTTATAAATCCAATTTCTGAAGGAATTAAACTTT
GGTTTAAGCCTCACATTACAAATTTGAATTAAGAAAGATCAGGTAGGTGCTCACATAC
CTTATACATGCAATTTCTGAAGGAATTAAACTTTGGTTTAAGCCTCACATTACAAATTT
GAATTAAGAAAGATTAACATATAATAGAATAAAATATTTCTAACTATTCCCATTTCAA
AGTAGATTTAGTTGGTTGTGGAGAAAGCCTATTTACCACGGAATCCTTCATTCTAATTT
TTTTTTTTTCTTTTAAGGCAAGAGAGGTTTAGAGCAAAGTCTAACAAAAAGATTAATAC
TACCAGATTACATATTGCAACTATTCCTTAAATACCACTATAAGTATTTATATAGAAGC
AGTCAGTTTGACAAGGAATTCTCAAGACTCAAGTATGTCTCATACTCTGCATTCCCTTT
CTCCATCTTTCAAAGGAGTTTAGTTTTCTG

FIG. 6.5

LTA4H_7908 (W=A/T)
GGAATCCTTCATTCTAATTTTTTTTTTTTTCTTTTAAGGCAAGAGAGGTTTAGAGCAAAG
TCTAACAAAAAGATTAATACTACCAGATTACATATTGCAACTATTCCTTAAATACCACT
ATAAGTATTTATATAGAAGCAGTCAGTTTGACAAGGAATTCTCAAGACTCAAGTATGT
CTCATACTCTGCATTCCCTTTCTCCATCTTTCAAAGGAGTTTAGTTTTCTGCTTTCTTCC
ACAGAGACAAGTTAAAATGATGTACCTGAATCGTATTTCAGAATTGTTAATGGCATTG
AAGTTGTACACCTCTTGCATTCGCTTTATGTGCCCCAATGGAAGAGGTGCCTAAGAGC
AAAATAAAGAAGTATACCGTATCATTTCAACAGGATTCCTTGGAAGAAAGGAGCTGG
AGAGAAATGCATAGCCAGATTAAAATCCTAAATATTTTATAATATAGAAATAAGTCAG
ATAAAAATAAAAGAAACAAATTGCACAC
[W]
AAGTAAATTCTGTGCAAACTTATTCCAGATGAGGATATTCTACTGGGAGCACAGGGAT
AATTTACTTTGTGAAGTATTCAGCATTAAATGAGAATTGCTCTTCTTAGACTTTTTAGC
ATGTATAAATATTATCTTTCAGACTTTTCCTAGAGTTTTTCTAGTTATTCTCTATAACTT
ATATATCTTAAATGCAATTCCATTCTCCAGATGAAATCATAGTTCCTTAATTTTTGCCT
GATTCCCCCTAGCTTTATCTTTGTATATTTCCTCTGAAATCCCTGTTAAATTATCTGCAT
ACCTACATAATAGCAGTTCTTAAATGTTTGTATTATAGATCTCTTTGGGAATCTGATGA
ATAATGTGGACTCTTTCCCTAGGGGGAAAATACACTTACTACATGAATACAAACTTCT
GTATACAATTTCAGGGGGTTTATAAGCATCCTATCCCTACCTTAACTCACCCTAAAAGG
GAGGACAAGTTTGGGTGAAGGAAAGAAA

LTA4H_8229 (K=G/T)
GCTTTATGTGCCCCAATGGAAGAGGTGCCTAAGAGCAAAATAAAGAAGTATACCGTAT
CATTTCAACAGGATTCCTTGGAAGAAAGGAGCTGGAGAGAAATGCATAGCCAGATTA
AAATCCTAAATATTTTATAATATAGAAATAAGTCAGATAAAAATAAAAGAAACAAATT
GCACACTAAGTAAATTCTGTGCAAACTTATTCCAGATGAGGATATTCTACTGGGAGCA
CAGGGATAATTTACTTTGTGAAGTATTCAGCATTAAATGAGAATTGCTCTTCTTAGACT
TTTTAGCATGTATAAATATTATCTTTCAGACTTTTCCTAGAGTTTTTCTAGTTATTCTCT
ATAACTTATATATCTTAAATGCAATTCCATTCTCCAGATGAAATCATAGTTCCTTAATT
TTTGCCTGATTCCCCCTAGCTTTATCTTTGTATATTTCCTCTGAAATCCCTGTTAAATTA
TCTGCATACCTACATAATAGCAGTTCTTAAA
[K]
GTTTGTATTATAGATCTCTTTGGGAATCTGATGAATAATGTGGACTCTTTCCCTAGGGG
GAAAATACACTTACTACATGAATACAAACTTCTGTATACAATTTCAGGGGGTTTATAA
GCATCCTATCCCTACCTTAACTCACCCTAAAAGGGAGGACAAGTTTGGGTGAAGGAAA
GAAAAAAGATGAGTTCAGTTTGGACAAGCAGAGAGTTTGTAGTGCCTGTGAGAGGCA
GAGGTGCCTCTAGGTAGATGATAACTCTCCCCTCCAACCACGACCTCCTTACCTTACAG
GACTCCACACTCACTAACCAATCTCTGCTTTCATGAACTACTAATCCTGTCGCTAATAA
TTTAGTCCATTAGCCCCTTATGGACACATGCAACTCCAAGTCTACCCTGGTAGACCAAC
TGGTTAAGGTCATCTCCAAGGCTCCCTGACTTGCCCTAAGTTTTGCTATACCCATTCCA
GAATCACCCTACCATGTTCTCTCTCTCTGTGG

LTA4H_8482 (R=A/G)
GTATTCAGCATTAAATGAGAATTGCTCTTCTTAGACTTTTTAGCATGTATAAATATTAT
CTTTCAGACTTTTCCTAGAGTTTTTCTAGTTATTCTCTATAACTTATATATCTTAAATGC
AATTCCATTCTCCAGATGAAATCATAGTTCCTTAATTTTTGCCTGATTCCCCCTAGCTTT
ATCTTTGTATATTTCCTCTGAAATCCCTGTTAAATTATCTGCATACCTACATAATAGCA
GTTCTTAAATGTTTGTATTATAGATCTCTTTGGGAATCTGATGAATAATGTGGACTCTT
TCCCTAGGGGGAAAATACACTTACTACATGAATACAAACTTCTGTATACAATTTCAGG
GGGTTTATAAGCATCCTATCCCTACCTTAACTCACCCTAAAAGGGAGGACAAGTTTGG
GTGAAGGAAAGAAAAAAGATGAGTTCAGTTTGGACAAGCAGAGAGTTTGTAGTGCCT
GTGAGAGGCAGAGGTGCCTCTAGGTAGATG
[R]
TAACTCTCCCCTCCAACCACGACCTCCTTACCTTACAGGACTCCACACTCACTAACCAA
TCTCTGCTTTCATGAACTACTAATCCTGTCGCTAATAATTTAGTCCATTAGCCCCTTATG
GACACATGCAACTCCAAGTCTACCCTGGTAGACCAACTGGTTAAGGTCATCTCCAAGG
CTCCCTGACTTGCCCTAAGTTTTGCTATACCCATTCCAGAATCACCCTACCATGTTCTCT
CTCTCTGTGGCCCTAGACCACCCACCAGTGGTAGAGCAATTTATGAAACCATGATGAC
CCGATGCACTAAAAATAGATTCTCTCTTTGATGGGTCCTTTGTTGCGTCAAAATCCTAT

FIG. 6.6

TCCTAATTTTTGCATCAATTCCACAGAAAATTCCGCTCCAAATCTTCTTTCTTCTCAAGG
TCCTTAGACTGAAGACTTCCCTTTCATGGAAGTCTTTAAAATCCAGTCATTGGTTTATC
TCAAAATGCAGCAACTCCTTTC

LTA4H_9587 (W=A/T)
TGTGTAAACTCTTTCTCACGTCCTGTTCTCTCCTCTCCCCGCAACTTACTCCCTCAAGTC
CGGTACTCCTGCCAGTCTCCCAACTAGTAACTTCACCACCATGCAACCTTCATGGCCCC
AGATTAGTTTTCTACAACCCAGCATTTCATCCCGACTCTTCTGCTGGATTTTTAAAATCT
TTTCCTACTGATCAGTGTAAGATCTAAAATTTCTTAGCTTAGCATTGAGAGTCATCACA
TCTGGTCCTACCAGCTTTTCTAGTGTTACCTTCACTGACTTCCTTACCCAGTGCTACTGT
TTACTCCAGCAATGCTGCAGACGAATTCCAGCCCTTGCTGCTCCCTCCACCTTCAATTT
CTACCTCCCTGCTAGCCCTGGGGGTGCAAAGCAAGTCTCCTCCAAAATTCCCTCTCTGA
TGCCCCCAGTTGGAAGAGTCTTTCACTAATTAAGTTTTCCAAATGATACCTAAAGTAT
GCCTCCTTTTATTGCTAATGTTTTT
[W]
AAAAAATTTTTTTATGAGATGGAGTTTCACTCTGTTGCTCAGGCTGGAGTACAGGGGT
GTGATCTCGGCTCACTGCAACCTCCGCCTCCCAGTCCAAGTGATTCTCCTGCCTCAGCC
TCCTGAGTAGCTGGGATTACAGGCACCTGCCACCATGCCCGGCTAATTTTTATATTTTT
AGTAGAGACGAGATTTCATCATGTTGGCCAGGCTGGTCTCGAACTCCTGACTTCAAGT
GATCTGCTTGCCTCGGCCTCCCAAAGTGCTGGGATTACAGATGTGAGCCACCGTGCCT
GGCTTATTGCTAAATTTTGCATGTGTTCCCCTTCCTACTAGATTATACGCTATTTGAAG
ATAAGGTATATCCTTTCTTACATATTTTCATATTTAGCACAATATAAAACACAGTAAGC
ATTCAATGCTTTTTTAAAGAAATGAATAAATTTTATAAATGATTTTTTCCCCATTAGTTT
CCACATTAATAATCTTTTGCCAAGTTGGGT

LTA4H_9759 (W=A/T)
ATCTTTTCCTACTGATCAGTGTAAGATCTAAAATTTCTTAGCTTAGCATTGAGAGTCAT
CACATCTGGTCCTACCAGCTTTTCTAGTGTTACCTTCACTGACTTCCTTACCCAGTGCTA
CTGTTTACTCCAGCAATGCTGCAGACGAATTCCAGCCCTTGCTGCTCCCTCCACCTTCA
ATTTCTACCTCCCTGCTAGCCCTGGGGGTGCAAAGCAAGTCTCCTCCAAAATTCCCTCT
CTGATGCCCCCAGTTGGAAGAGTCTTTCACTAATTAAGTTTTCCAAATGATACCTAAA
GTATGCCTCCTTTTATTGCTAATGTTTTTAAAAAAATTTTTTTATGAGATGGAGTTTCAC
TCTGTTGCTCAGGCTGGAGTACAGGGGTGTGATCTCGGCTCACTGCAACCTCCGCCTCC
CAGTCCAAGTGATTCTCCTGCCTCAGCCTCCTGAGTAGCTGGGATTACAGGCACCTGCC
ACCATGCCCGGCTAATTTTTATA
[W]
TTTTAGTAGAGACGAGATTTCATCATGTTGGCCAGGCTGGTCTCGAACTCCTGACTTCA
AGTGATCTGCTTGCCTCGGCCTCCCAAAGTGCTGGGATTACAGATGTGAGCCACCGTG
CCTGGCTTATTGCTAAATTTTGCATGTGTTCCCCTTCCTACTAGATTATACGCTATTTGA
AGATAAGGTATATCCTTTCTTACATATTTTCATATTTAGCACAATATAAAACACAGTAA
GCATTCAATGCTTTTTTAAAGAAATGAATAAATTTTATAAATGATTTTTTCCCCATTAG
TTTCCACATTAATAATCTTTTGCCAAGTTGGGTAGAACATAAATGCTGTGCCTTTCTGT
CCATTTTAATTTCTAAGATTTTGAGCTAGTACTTACCCTCTGGAGCGTCTGTGCTAAAA
ACTCATTCAATTGATGAGAAGAGAGATCCTTCAGGTCTGTGGCATTGAATGAATTTAA
ATCATCTTCTTTGGCCTGAAATAAATGTT

LTA4H_9927 (M=A/C)
ACCTTCAATTTCTACCTCCCTGCTAGCCCTGGGGGTGCAAAGCAAGTCTCCTCCAAAAT
TCCCTCTCTGATGCCCCCAGTTGGAAGAGTCTTTCACTAATTAAGTTTTCCAAATGAT
ACCTAAAGTATGCCTCCTTTTATTGCTAATGTTTTTAAAAAAATTTTTTTATGAGATGG
AGTTTCACTCTGTTGCTCAGGCTGGAGTACAGGGGTGTGATCTCGGCTCACTGCAACCT
CCGCCTCCCAGTCCAAGTGATTCTCCTGCCTCAGCCTCCTGAGTAGCTGGGATTACAGG
CACCTGCCACCATGCCCGGCTAATTTTTATATTTTTAGTAGAGACGAGATTTCATCATG
TTGGCCAGGCTGGTCTCGAACTCCTGACTTCAAGTGATCTGCTTGCCTCGGCCTCCCAA
AGTGCTGGGATTACAGATGTGAGCCACCGTGCCTGGCTTATTGCTAAATTTTGCATGTG
TTCCCCTTCCTACTAGATTATA
[M]
GCTATTTGAAGATAAGGTATATCCTTTCTTACATATTTTCATATTTAGCACAATATAAA
ACACAGTAAGCATTCAATGCTTTTTTAAAGAAATGAATAAATTTTATAAATGATTTTTT

FIG. 6.7

CCCCATTAGTTTCCACATTAATAATCTTTTGCCAAGTTGGGTAGAACATAAATGCTGTG
CCTTTCTGTCCATTTTAATTTCTAAGATTTTGAGCTAGTACTTACCCTCTGGAGCGTCTG
TGCTAAAAACTCATTCAATTGATGAGAAGAGAGATCCTTCAGGTCTGTGGCATTGAAT
GAATTTAAATCATCTTCTTTGGCCTGAAATAAATGTTACCTAGTTATTTTTGTTCAAGT
ACAATTTAATAATACTTATTGGTTTATCTGACATAAAAGTAAAAATTGAGAAAAAGAA
CCATATGAATGAACAAGATTATTCAAAATAAATTTAAGCCTGAGTTACTTAAATAATC
CTGAGATTGAGTTACTGTAATTTAAATAGC

LTA4H_10044 (Y=C/T)
TGATACCTAAAGTATGCCTCCTTTTATTGCTAATGTTTTTAAAAAAATTTTTTTATGAGA
TGGAGTTTCACTCTGTTGCTCAGGCTGGAGTACAGGGGTGTGATCTCGGCTCACTGCA
ACCTCCGCCTCCCAGTCCAAGTGATTCTCCTGCCTCAGCCTCCTGAGTAGCTGGGATTA
CAGGCACCTGCCACCATGCCCGGCTAATTTTTATATTTTTAGTAGAGACGAGATTTCAT
CATGTTGGCCAGGCTGGTCTCGAACTCCTGACTTCAAGTGATCTGCTTGCCTCGGCCTC
CCAAAGTGCTGGGATTACAGATGTGAGCCACCGTGCCTGGCTTATTGCTAAATTTTGC
ATGTGTTCCCCTTCCTACTAGATTATACGCTATTTGAAGATAAGGTATATCCTTTCTTAC
ATATTTTCATATTTAGCACAATATAAAACACAGTAAGCATTCAATGCTTTTTAAAGAA
ATGAATAAATTTTATAAATGATTTT
[Y]
TCCCCATTAGTTTCCACATTAATAATCTTTTGCCAAGTTGGGTAGAACATAAATGCTGT
GCCTTTCTGTCCATTTTAATTTCTAAGATTTTGAGCTAGTACTTACCCTCTGGAGCGTCT
GTGCTAAAAACTCATTCAATTGATGAGAAGAGAGATCCTTCAGGTCTGTGGCATTGAA
TGAATTTAAATCATCTTCTTTGGCCTGAAATAAATGTTACCTAGTTATTTTTGTTCAAGT
ACAATTTAATAATACTTATTGGTTTATCTGACATAAAAGTAAAAATTGAGAAAAAGAA
CCATATGAATGAACAAGATTATTCAAAATAAATTTAAGCCTGAGTTACTTAAATAATC
CTGAGATTGAGTTACTGTAATTTAAATAGCTGATATGACTCCTAGAATCTATATTACTT
AAGAAAAAGTAGATTATGGGTAGGAAGAGTGGAAGAAACTGTTGACATTCATTGTAC
CATTCGAGGTATAGAAATTTCCAAAGCAAAG

LTA4H_10518 (Y=C/T)
AATGAATAAATTTTATAAATGATTTTTTCCCCATTAGTTTCCACATTAATAATCTTTTGC
CAAGTTGGGTAGAACATAAATGCTGTGCCTTTCTGTCCATTTTAATTTCTAAGATTTTG
AGCTAGTACTTACCCTCTGGAGCGTCTGTGCTAAAAACTCATTCAATTGATGAGAAGA
GAGATCCTTCAGGTCTGTGGCATTGAATGAATTTAAATCATCTTCTTTGGCCTGAAATA
AATGTTACCTAGTTATTTTTGTTCAAGTACAATTTAATAATACTTATTGGTTTATCTGAC
ATAAAAGTAAAAATTGAGAAAAAGAACCATATGAATGAACAAGATTATTCAAAATAA
ATTTAAGCCTGAGTTACTTAAATAATCCTGAGATTGAGTTACTGTAATTTAAATAGCTG
ATATGACTCCTAGAATCTATATTACTTAAGAAAAAGTAGATTATGGGTAGGAAGAGTG
GAAGAAACTGTTGACATTCATTGTACCATT
[Y]
GAGGTATAGAAATTTCCAAAGCAAAGAAACATTTCAAAATGTATGCATGTCAACTAAT
CTATAGACCAATTCAAAAAGGTAAAGAATGAAATCGTATATTTTTAAATATTACATTA
ATAAATTGGTAAGGCCATAAACTAATGTTTTCCTCCATCCCCACATATTCTGTTTTCCC
CACTTAATCTTAGAAACCATCTAAGAAAAATAAAAATGAGTCTGCACTTTTCAAATTT
GGATTTACTCTCAAAAATCTTTGAGAAGATGATTAAGCAATATTAAATAAAGCTTATA
AAAATAAGGATTTTTAAATCTTTTAGAACTACTTTTATAATCTTTTAAACTAGGGCTTT
TGTTACTTTAAAAGAAATATATGCAAATACTAAAAAATCAAATAGGACAGAAGGAAA
AATTCTTTTGGATCTGCTCCCTGTCTCCAAGTACTACTCCTCAGTAACTAATATTAGTA
GTTTCTGTATATCCTTCCACTAAATTTAATGCAT

LTA4H_10627 (W=A/T)
GATTTTGAGCTAGTACTTACCCTCTGGAGCGTCTGTGCTAAAAACTCATTCAATTGATG
AGAAGAGAGATCCTTCAGGTCTGTGGCATTGAATGAATTTAAATCATCTTCTTTGGCCT
GAAATAAATGTTACCTAGTTATTTTTGTTCAAGTACAATTTAATAATACTTATTGGTTT
ATCTGACATAAAAGTAAAAATTGAGAAAAAGAACCATATGAATGAACAAGATTATTC
AAAATAAATTTAAGCCTGAGTTACTTAAATAATCCTGAGATTGAGTTACTGTAATTTAA
ATAGCTGATATGACTCCTAGAATCTATATTACTTAAGAAAAAGTAGATTATGGGTAGG
AAGAGTGGAAGAAACTGTTGACATTCATTGTACCATTCGAGGTATAGAAATTTCCAAA

FIG. 6.8

GCAAAGAAACATTTCAAAATGTATGCATGTCAACTAATCTATAGACCAATTCAAAAAG
GTAAAGAATGAAATCGTATATTTTTAAATA
[W]
TACATTAATAAATTGGTAAGGCCATAAACTAATGTTTTCCTCCATCCCCACATATTCTG
TTTTCCCCACTTAATCTTAGAAACCATCTAAGAAAAATAAAAATGAGTCTGCACTTTTC
AAATTTGGATTTACTCTCAAAAATCTTTGAGAAGATGATTAAGCAATATTAAATAAAG
CTTATAAAAATAAGGATTTTTAAATCTTTTAGAACTACTTTTATAATCTTTTAAACTAG
GGCTTTTGTTACTTTAAAAGAAATATATGCAAATACTAAAAAATCAAATAGGACAGAA
GGAAAAATTCTTTTGGATCTGCTCCCTGTCTCCAAGTACTACTCCTCAGTAACTAATAT
TAGTAGTTTCTGTATATCCTTCCACTAAATTTAATGCATAGGTATATACCCTTTTAAAT
AAATATTTTGCATCTTCCCCCTCTTCAGAACTCTCTTTAATAGCAATACTTCTTTTCCCT
TTACAACTTATCCTTAATATGAGAACTTA

LTA4H_10890 (Y=C/Y)
AAATAATCCTGAGATTGAGTTACTGTAATTTAAATAGCTGATATGACTCCTAGAATCTA
TATTACTTAAGAAAAAGTAGATTATGGGTAGGAAGAGTGGAAGAAACTGTTGACATTC
ATTGTACCATTCGAGGTATAGAAATTTCCAAAGCAAAGAAACATTTCAAAATGTATGC
ATGTCAACTAATCTATAGACCAATTCAAAAAGGTAAAGAATGAAATCGTATATTTTTA
AATATTACATTAATAAATTGGTAAGGCCATAAACTAATGTTTTCCTCCATCCCCACATA
TTCTGTTTTCCCCACTTAATCTTAGAAACCATCTAAGAAAAATAAAAATGAGTCTGCAC
TTTTCAAATTTGGATTTACTCTCAAAAATCTTTGAGAAGATGATTAAGCAATATTAAAT
AAAGCTTATAAAAATAAGGATTTTTAAATCTTTTAGAACTACTTTTATAATCTTTTAAA
CTAGGGCTTTTGTTACTTTAAAAGAAATATA
[Y]
GCAAATACTAAAAAATCAAATAGGACAGAAGGAAAAATTCTTTTGGATCTGCTCCCTG
TCTCCAAGTACTACTCCTCAGTAACTAATATTAGTAGTTTCTGTATATCCTTCCACTAA
ATTTAATGCATAGGTATATACCCTTTTAAATAAATATTTTGCATCTTCCCCCTCTTCAGA
ACTCTCTTTAATAGCAATACTTCTTTTCCCTTTACAACTTATCCTTAATATGAGAACTTA
CAGCTCCAGCTCATTTTCTGTGCAAAAACCTGCAAATCTAAACTATATATTAATTAAGG
ATATATTTATGTGGTAAAAACATAAAAAGCAAGAGAATGATAAACCAAAATTCAGGA
CAATGGTAACCTGGATGGGTCAGCAAGGAGGGTGGAGAGGGGCATAAGATGGGGAGG
GATGCTACAGAGGTACCGCTAAGATTTTACTTCTTATGCTAGTGGTGGGTCACACAATT
GTTTTATACACCATATGAATATGTTATAAAT

LTA4H_11208 (M=A/C)
AACCATCTAAGAAAAATAAAAATGAGTCTGCACTTTTCAAATTTGGATTTACTCTCAA
AAATCTTTGAGAAGATGATTAAGCAATATTAAATAAAGCTTATAAAAATAAGGATTTT
TAAATCTTTTAGAACTACTTTTATAATCTTTTAAACTAGGGCTTTTGTTACTTTAAAAGA
AATATATGCAAATACTAAAAAATCAAATAGGACAGAAGGAAAAATTCTTTTGGATCTG
CTCCCTGTCTCCAAGTACTACTCCTCAGTAACTAATATTAGTAGTTTCTGTATATCCTTC
CACTAAATTTAATGCATAGGTATATACCCTTTTAAATAAATATTTTGCATCTTCCCCCT
CTTCAGAACTCTCTTTAATAGCAATACTTCTTTTCCCTTTACAACTTATCCTTAATATGA
GAACTTACAGCTCCAGCTCATTTTCTGTGCAAAAACCTGCAAATCTAAACTATATATTA
ATTAAGGATATATTTATGTGGTAAAAAC
[M]
TAAAAAGCAAGAGAATGATAAACCAAAATTCAGGACAATGGTAACCTGGATGGGTCA
GCAAGGAGGGTGGAGAGGGGCATAAGATGGGGAGGGATGCTACAGAGGTACCGCTA
AGATTTTACTTCTTATGCTAGTGGTGGGTCACACAATTGTTTTATACACCATATGAATA
TGTTATAAATATTCTTTTGCATTTATTTACTATTTAAGACAAATCATTGAGAAATAAAA
TACATAAGGAAAAGAGTGCATTAGTGAATACAGTGTCCTGAATCTGTTCCTAACAATG
CCTGTTTCTACTAATATTGAAGAGTTGATCATTATCCACCTTAACTGCTGGGCCCAAAG
GAATATTTGAGCAGAAATTAGTAGCAGTTTTAACTAGCACCAAATAAGCTGGAATACA
TTTTTCAAACTAAAACAGAGAATTTTAATACACTCACACTGTTAAAAAATCCTGTTTCC
CATAGAAATCTCTTATACTTTTCTTCATGACAAGT

LTA4H_11310 / SG12S21 (R=A/G)
AATAAGGATTTTTAAATCTTTTAGAACTACTTTTATAATCTTTTAAACTAGGGCTTTTGT
TACTTTAAAAGAAATATATGCAAATACTAAAAAATCAAATAGGACAGAAGGAAAAAT
TCTTTTGGATCTGCTCCCTGTCTCCAAGTACTACTCCTCAGTAACTAATATTAGTAGTTT

FIG. 6.9

CTGTATATCCTTCCACTAAATTTAATGCATAGGTATATACCCTTTTAAATAAATATTTT
GCATCTTCCCCCTCTTCAGAACTCTCTTTAATAGCAATACTTCTTTTCCCTTTACAACTT
ATCCTTAATATGAGAACTTACAGCTCCAGCTCATTTTCTGTGCAAAAACCTGCAAATCT
AAACTATATATTAATTAAGGATATATTTATGTGGTAAAAACATAAAAAGCAAGAGAAT
GATAAACCAAAATTCAGGACAATGGTAACCTGGATGGGTCAGCAAGGAGGGTGGAGA
GGGGCATAAGATGGGGAGGGATGCTACA
[R]
AGGTACCGCTAAGATTTTACTTCTTATGCTAGTGGTGGGTCACACAATTGTTTTATACA
CCATATGAATATGTTATAAATATTCTTTTGCATTTATTTACTATTTAAGACAAATCATTG
AGAAATAAAATACATAAGGAAAAGAGTGCATTAGTGAATACAGTGTCCTGAATCTGTT
CCTAACAATGCCTGTTTCTACTAATATTGAAGAGTTGATCATTATCCACCTTAACTGCT
GGGCCCAAAGGAATATTTGAGCAGAAATTAGTAGCAGTTTTAACTAGCACCAAATAAG
CTGGAATACATTTTTCAAACTAAAACAGAGAATTTTAATACACTCACACTGTTAAAAA
ATCCTGTTTCCCATAGAAATCTCTTATACTTTTCTTCATGACAAGTTTGTCAACTACACA
AAACAGGTTTTAAAAGGCAATAGCTGAACTGATTGCACAGCTGGAGGCCATTATCCTA
AGTGAATTAACACAGGAACAGAAAACC

LTA4H_12592 (Y=C/T)
TTATTTTTCATTAAAGAATTATCAAGGGCTCATCCTTACTTTGGCTTCAGTAAAGGGTT
CTATTTTAGTACATATATGAAGAAGCTCCTCTTTAAGAAGCTTCATAGAAAGTGAACA
AAGAGCAAAAGTGCTTCGATTCTTTGCACCACTAATAGTCAGCAGCTGGTCACCCAAG
ATCATTTTAGATTTACCTGGTATGTGAAATTGCCATATTGGAAGCAGTATCTTATAAAT
GATTTAAAAGGAAAAGAAGAAAGGTAAGATGCAAATATTTTTGCATACTTTTTTTTTT
AAGAGTTAAGAAGCAAGAAAAAATCAGGATTAATGCCTTCAACATCAATTTTTCCCCCC
ATAAAACTTAATTTTCTAGGCTGGGCACAGTGGCTCATGCCTGATGCCTGTAATTCCAG
CACTTTGGGAGGCTAAGGTGGGAGGATCACTGGAGACCAGGAGTTTGAGACCAGCCT
GTACAACACAGACCCTGTTTGTA
[Y]
AAAAAGTTTTAAATTAGCCAGGCATGGAGGCACATGCCTGTAGTCCCAGTTACTCGGG
AGGCTGAGGTGGGACAACTGACTGAGCCCAGGAGGTTGAGGCTGCAATGAGCCATGA
TCACGCCACTGTAGTCCAGCCTGGGCAACAGAGCAAGACCCTGTCTCAAACCCTTAAT
TTTCTATATTGAGAGTAGATATAATATCACCTTAGATAAACCTGACTTTCAAATAGCCT
TTCCAAATATAACTGTTTGTGATTTAAAGTACCCTCCCTGCTTCATGAGTAAAGACATA
TTTGCACAATTCAAAAAGGAATCAAAAATCACACATTATTACTTACAGTAATCCATCTT
TGACTTAAGGCAATACAAGCATTTGTCAGAGTCATATCATAACTGCAAAGATAAAGAT
TACATTGTTTAAAAATGCACGTGCTTTTGCAGAAATGCAGTTTTAAAGCTACAGTACAT
ACTTAAATTTCAAAGTCCC

LTA4H_12806 (Y=C/T)
TATCTTATAAATGATTTAAAAGGAAAAGAAGAAAGGTAAGATGCAAATATTTTTGCAT
ACTTTTTTTTTTTAAGAGTTAAGAAGCAAGAAAAAATCAGGATTAATGCCTTCAACATCA
ATTTTTCCCCCCATAAAACTTAATTTTCTAGGCTGGGCACAGTGGCTCATGCCTGATGC
CTGTAATTCCAGCACTTTGGGAGGCTAAGGTGGGAGGATCACTGGAGACCAGGAGTTT
GAGACCAGCCTGTACAACACAGACCCTGTTTGTATAAAAAGTTTTAAATTAGCCAGGC
ATGGAGGCACATGCCTGTAGTCCCAGTTACTCGGGAGGCTGAGGTGGGACAACTGACT
GAGCCCAGGAGGTTGAGGCTGCAATGAGCCATGATCACGCCACTGTAGTCCAGCCTGG
GCAACAGAGCAAGACCCTGTCTCAAACCCTTAATTTTCTATATTGAGAGTAGATATAA
TATCACCTTAGATAAA
[Y]
CTGACTTTCAAATAGCCTTTCCAAATATAACTGTTTGTGATTTAAAGTACCCTCCCTGC
TTCATGAGTAAAGACATATTTGCACAATTCAAAAAGGAATCAAAAATCACACATTATT
ACTTACAGTAATCCATCTTTGACTTAAGGCAATACAAGCATTTGTCAGAGTCATATCAT
AACTGCAAAGATAAAGATTACATTGTTTAAAAATGCACGTGCTTTTGCAGAAATGCAG
TTTTAAAGCTACAGTACATACTTAAATTTCAAAGTCCCTTTTAAATAAGGAAAACAAA
CTCCAAAGTGAGGAAAATAGGAAATATTTTACCTAACTTACATACTACTGGCATCATC
CAAGAACTCACAAACCCAAATGGATACCACATTAATGAAACACCCATCTATCTTTTAG
AAAGAATGCCAAAGCACCTCAGCAAAAGACTGTCATGTGCTCGAGTAGTATATGCTAA
AGTAGTTGGAATCAGTTGAGCATAT

FIG. 6.10

LTA4H_13257 / SG12S22 (V=A/G/C)
TTTTCTATATTGAGAGTAGATATAATATCACCTTAGATAAACCTGACTTTCAAATAGCC
TTTCCAAATATAACTGTTTGTGATTTAAAGTACCCTCCCTGCTTCATGAGTAAAGACAT
ATTTGCACAATTCAAAAAGGAATCAAAAATCACACATTATTACTTACAGTAATCCATC
TTTGACTTAAGGCAATACAAGCATTTGTCAGAGTCATATCATAACTGCAAAGATAAAG
ATTACATTGTTTAAAAATGCACGTGCTTTTGCAGAAATGCAGTTTTAAAGCTACAGTAC
ATACTTAAATTTCAAAGTCCCTTTTAAATAAGGAAAACAAACTCCAAAGTGAGGAAAA
TAGGAAATATTTTACCTAACTTACATACTACTGGCATCATCCAAGAACTCACAAACCC
AAATGGATACCACATTAATGAAACACCCATCTATCTTTTAGAAAGAATGCCAAAGCAC
CTCAGCAAAAGACTGTCATGTGCTC
[V]
AGTAGTATATGCTAAAGTAGTTGGAATCAGTTGAGCATATTTAGTACATGGCAGGAAC
AGTTCTAGGCACTCAAGACAACAAGATGAACAACATCAAGTCCTTGCTGTCATGGATT
TTACTTGGTTGTTCCAAACATCTAATCATCTAACAAACCTGCAAGCACCTGCTACATAA
TTGGCACCGTTCTAGATGCTAGACCCTTGAGAGAGCCCGATACCATTGCCTGATGATTT
CATTCCTTTTTAGAAGAAAATGAAATTAACACATGGTAATTGTTAAGCAAATTATACC
AATATTTGTGTGTTCTCAACTTAGAAATCATATTTTGCAACAATGGGAAAGAACATGT
AGTGTGTGCAAAATTCTTGCAAAACATCCCTCTTTCTCCGTAAATCATGCTTGCTTGTA
CTGAAATGCTTGTATTAGGGAACAGAGAGGCACCTGCCCCTTAGAGCCTAAATGAAGT
AAGTTTTGATTAGAAGTTACCACT

LTA4H_13411 (Y=C/T)
ACTTACAGTAATCCATCTTTGACTTAAGGCAATACAAGCATTTGTCAGAGTCATATCAT
AACTGCAAAGATAAAGATTACATTGTTTAAAAATGCACGTGCTTTTGCAGAAATGCAG
TTTTAAAGCTACAGTACATACTTAAATTTCAAAGTCCCTTTTAAATAAGGAAAACAAA
CTCCAAAGTGAGGAAAATAGGAAATATTTTACCTAACTTACATACTACTGGCATCATC
CAAGAACTCACAAACCCAAATGGATACCACATTAATGAAACACCCATCTATCTTTTAG
AAAGAATGCCAAAGCACCTCAGCAAAAGACTGTCATGTGCTCGAGTAGTATATGCTAA
AGTAGTTGGAATCAGTTGAGCATATTTAGTACATGGCAGGAACAGTTCTAGGCACTCA
AGACAACAAGATGAACAACATCAAGTCCTTGCTGTCATGGATTTTACTTGGTTGTTCCA
AACATCTAATCATCTAACAAA
[Y]
CTGCAAGCACCTGCTACATAATTGGCACCGTTCTAGATGCTAGACCCTTGAGAGAGCC
CGATACCATTGCCTGATGATTTCATTCCTTTTTAGAAGAAAATGAAATTAACACATGGT
AATTGTTAAGCAAATTATACCAATATTTGTGTGTTCTCAACTTAGAAATCATATTTTGC
AACAATGGGAAAGAACATGTAGTGTGTGCAAAATTCTTGCAAAACATCCCTCTTTCTC
CGTAAATCATGCTTGCTTGTACTGAAATGCTTGTATTAGGGAACAGAGAGGCACCTGC
CCCTTAGAGCCTAAATGAAGTAAGTTTTGATTAGAAGTTACCACTGAATCTCCCTTAAA
GAGAGTTGTGACTGGGACTCCGTTTGTTCCCTAGGGGAGACAATAAAAAGGTCAACAC
AGCTCCCACCTCGAAGCAGCTGCCAGTTTATTACATGAAGTGTCAGGCTGTGGACTGC
AGGCATGCCATTTTGTCTTCAAGAACAGGTGGG

LTA4H_13668 / SG12S23 (Y=C/T)
TGGATACCACATTAATGAAACACCCATCTATCTTTTAGAAAGAATGCCAAAGCACCTC
AGCAAAAGACTGTCATGTGCTCGAGTAGTATATGCTAAAGTAGTTGGAATCAGTTGAG
CATATTTAGTACATGGCAGGAACAGTTCTAGGCACTCAAGACAACAAGATGAACAAC
ATCAAGTCCTTGCTGTCATGGATTTTACTTGGTTGTTCCAAACATCTAATCATCTAACA
AACCTGCAAGCACCTGCTACATAATTGGCACCGTTCTAGATGCTAGACCCTTGAGAGA
GCCCGATACCATTGCCTGATGATTTCATTCCTTTTTAGAAGAAAATGAAATTAACACAT
GGTAATTGTTAAGCAAATTATACCAATATTTGTGTGTTCTCAACTTAGAAATCATATTT
TGCAACAATGGGAAAGAACATGTAGTGTGTGCAAAATTCTTGCAAAACATCCCTCTTT
CTCCGTAAATCATGCTTGCTTGTAC
[Y]
GAAATGCTTGTATTAGGGAACAGAGAGGCACCTGCCCCTTAGAGCCTAAATGAAGTAA
GTTTTGATTAGAAGTTACCACTGAATCTCCCTTAAAGAGAGTTGTGACTGGGACTCCGT
TTGTTCCCTAGGGGAGACAATAAAAAGGTCAACACAGCTCCCACCTCGAAGCAGCTGC
CAGTTTATTACATGAAGTGTCAGGCTGTGGACTGCAGGCATGCCATTTTGTCTTCAAGA
ACAGGTGGGATCAGAGGTCCTTGACTGATCAGAATACACTGCTTTCAACCAAAACATT
ATTAGCATTGATTTCTTAAAAAATAATAGCAAAGTAGAAAACCTTTAGCTGGTCTGTTT

FIG. 6.11

CTTCGTGTCCTGAAACTTCCTTATTAGTGTAATTAAAAGTACTAAGTTAAGAATTAGCC
TGGGAAAGGACCCTACTTATGGCAAAGTCTTCAGAAAAGTAAAGAGCAAAACCAGAT
ATGTGCCTTGTTCTCATGGTGCTGACAGTATAG

LTA4H_13952 (Y=C/T)
GAGCCCGATACCATTGCCTGATGATTTCATTCCTTTTTAGAAGAAAATGAAATTAACAC
ATGGTAATTGTTAAGCAAATTATACCAATATTTGTGTGTTCTCAACTTAGAAATCATAT
TTTGCAACAATGGGAAAGAACATGTAGTGTGTGCAAAATTCTTGCAAAACATCCCTCT
TTCTCCGTAAATCATGCTTGCTTGTACTGAAATGCTTGTATTAGGGAACAGAGAGGCA
CCTGCCCCTTAGAGCCTAAATGAAGTAAGTTTTGATTAGAAGTTACCACTGAATCTCCC
TTAAAGAGAGTTGTGACTGGGACTCCGTTTGTTCCCTAGGGGAGACAATAAAAAGGTC
AACACAGCTCCCACCTCGAAGCAGCTGCCAGTTTATTACATGAAGTGTCAGGCTGTGG
ACTGCAGGCATGCCATTTTGTCTTCAAGAACAGGTGGGATCAGAGGTCCTTGACTGAT
CAGAATACACTGCTTTCAAC
[Y]
AAAACATTATTAGCATTGATTTCTTAAAAAATAATAGCAAAGTAGAAAACCTTTAGCT
GGTCTGTTTCTTCGTGTCCTGAAACTTCCTTATTAGTGTAATTAAAAGTACTAAGTTAA
GAATTAGCCTGGGAAAGGACCCTACTTATGGCAAAGTCTTCAGAAAAGTAAAGAGCA
AAACCAGATATGTGCCTTGTTCTCATGGTGCTGACAGTATAGCGAAGAGGAAATACTT
TAATCATACGAATAAATAAATGTAAAGTTAGAACTGTGCAACTGCTACGAAGAGAGG
ATATAGCACTAAAAAGCCCTAGAATGGGAGATTTGACCTGGCCAGGGATGTCAAGAA
ATGCTTCCAAGAGGAAGTGGTTCTTGAGCTGAGATTGGAATTAACTGGGCAAAGGGCT
CCGGGTAGAGAAAACAGCATGCTCAGGTACTATGTTGGAGGACATATGGGGAGTTCG
AGAAACTCCAAAACTGCCAGTGTGACTGAAGCAAAGGGA

LTA4H_14047 (W=A/T)
TCTCAACTTAGAAATCATATTTTGCAACAATGGGAAAGAACATGTAGTGTGTGCAAAA
TTCTTGCAAAACATCCCTCTTTCTCCGTAAATCATGCTTGCTTGTACTGAAATGCTTGTA
TTAGGGAACAGAGAGGCACCTGCCCCTTAGAGCCTAAATGAAGTAAGTTTTGATTAGA
AGTTACCACTGAATCTCCCTTAAAGAGAGTTGTGACTGGGACTCCGTTTGTTCCCTAGG
GGAGACAATAAAAAGGTCAACACAGCTCCCACCTCGAAGCAGCTGCCAGTTTATTACA
TGAAGTGTCAGGCTGTGGACTGCAGGCATGCCATTTTGTCTTCAAGAACAGGTGGGAT
CAGAGGTCCTTGACTGATCAGAATACACTGCTTTCAACCAAAACATTATTAGCATTGA
TTTCTTAAAAAATAATAGCAAAGTAGAAAACCTTTAGCTGGTCTGTTTCTTCGTGTCCT
GAAACTTCCTTATTAG
[W]
GTAATTAAAAGTACTAAGTTAAGAATTAGCCTGGGAAAGGACCCTACTTATGGCAAAG
TCTTCAGAAAAGTAAAGAGCAAAACCAGATATGTGCCTTGTTCTCATGGTGCTGACAG
TATAGCGAAGAGGAAATACTTTAATCATACGAATAAATAAATGTAAAGTTAGAACTGT
GCAACTGCTACGAAGAGAGGATATAGCACTAAAAAGCCCTAGAATGGGAGATTTGAC
CTGGCCAGGGATGTCAAGAAATGCTTCCAAGAGGAAGTGGTTCTTGAGCTGAGATTGG
AATTAACTGGGCAAAGGGCTCCGGGTAGAGAAAACAGCATGCTCAGGTACTATGTTG
GAGGACATATGGGGAGTTCGAGAAACTCCAAAACTGCCAGTGTGACTGAAGCAAAGG
GAGCTAGAGTGTTAGGAGCTTATAATCCCCACTAAAGGATTTTGTCTTAGCCCAAGAG
CAAAGAGATACCAGTGGAGACTGCTAAGCAGGAGGACAA

LTA4H_14333 (W=A/T)
CATGAAGTGTCAGGCTGTGGACTGCAGGCATGCCATTTTGTCTTCAAGAACAGGTGGG
ATCAGAGGTCCTTGACTGATCAGAATACACTGCTTTCAACCAAAACATTATTAGCATT
GATTTCTTAAAAAATAATAGCAAAGTAGAAAACCTTTAGCTGGTCTGTTTCTTCGTGTC
CTGAAACTTCCTTATTAGTGTAATTAAAAGTACTAAGTTAAGAATTAGCCTGGGAAAG
GACCCTACTTATGGCAAAGTCTTCAGAAAAGTAAAGAGCAAAACCAGATATGTGCCTT
GTTCTCATGGTGCTGACAGTATAGCGAAGAGGAAATACTTTAATCATACGAATAAATA
AATGTAAAGTTAGAACTGTGCAACTGCTACGAAGAGAGGATATAGCACTAAAAAGCC
CTAGAATGGGAGATTTGACCTGGCCAGGGATGTCAAGAAATGCTTCCAAGAGGAAGT
GGTTCTTGAGCTGAGA
[W]
GAATTAACTGGGCAAAGGGCTCCGGGTAGAGAAAACAGCATGCTCAGGTACTATGTT
GGAGGACATATGGGGAGTTCGAGAAACTCCAAAACTGCCAGTGTGACTGAAGCAAAG

FIG. 6.12

GGAGCTAGAGTGTTAGGAGCTTATAATCCCCACTAAAGGATTTTGTCTTAGCCCAAGA
GCAAAGAGATACCAGTGGAGACTGCTAAGCAGGAGGACAACATGACACATTTGTGCT
TTTAAAGGTTTACTCTAGCTTTAGTGTGGAGAGTGGCTGGGAGAAGTCAGAACAGATA
CAAGTGCACAGTTTGGGTGCCAGAACAGTCTTCCAGGATGTGAAGATGTGATACTGAA
CTTGGACAGTGGTAGTAGAAATGGAGAGATGTGGATAGACTCAGATATTTAAATACAT
ATACAAATGATGAGAGCATTATAAAAAGAGGATCGTGGAAGCCAAGATTCTGTGCTG
CAATGGATCAAAGTATTTTCTGTGGTTTGAGATTTTCT

LTA4H_14965 (Y=C/T)
GGATTTTGTCTTAGCCCAAGAGCAAAGAGATACCAGTGGAGACTGCTAAGCAGGAGG
ACAACATGACACATTTGTGCTTTTAAAGGTTTACTCTAGCTTTAGTGTGGAGAGTGGCT
GGGAGAAGTCAGAACAGATACAAGTGCACAGTTTGGGTGCCAGAACAGTCTTCCAGG
ATGTGAAGATGTGATACTGAACTTGGACAGTGGTAGTAGAAATGGAGAGATGTGGAT
AGACTCAGATATTTAAATACATATACAAATGATGAGAGCATTATAAAAAGAGGATCGT
GGAAGCCAAGATTCTGTGCTGCAATGGATCAAAGTATTTTCTGTGGTTTGAGATTTTCT
AAGATACTCTCTCTTTACAGAATTCCCGGGCACACGAATGATTCCAGGGTTCCTCCAGC
ACTTTGGTATTACTTGAAAGCAATCTTAAGGGATCTAGAATGAACCAACGCCCAAAAA
GGATCCCTTAGCAG
[Y]
GGTGATATCAAAGAAACACTTTTGAAGAACTAATTTTCCACCCAGATTTCCCCAATTTT
AAAAGCAATGGGCAAAGCCTTCTCCACTCCTAAACTTCCTGGAACTGTCTTTTGGCTAT
ATCAGGCCCCTGAAGTTAGAGTCTTTGAAAGACTCCAAACTCCAAATTCTATGCTTTTA
TTCTCAGGCTCCTCATAATTCTACAGCACACCAGACTGCTGACCACTCTCCGTACCACT
TTTAAATTATTTCTTCCCACAGCTTTCTTAACAATGAACCTTTGAAATCTTTTTAGTTTT
CCATTTATTTTGCTACCTTTCCTCTGTCCTAGCTCTAAAATGAAGATCCTCTAAGGTTCT
ACAGTTTACTTCTTGTATTCTCCTTTGTAAGTCATCTCCAAGACGATGTCCAAATCCAT
CACCATTAAAATTAATAGTTTCCTCACCCACAACACTTAATATTTTAAAAAAAATACTT
TTCATTGTATTATAATTACTTGATAC

LTA4H_15135 / SG12S24 (Y=C/T)
TCTTCCAGGATGTGAAGATGTGATACTGAACTTGGACAGTGGTAGTAGAAATGGAGAG
ATGTGGATAGACTCAGATATTTAAATACATATACAAATGATGAGAGCATTATAAAAAG
AGGATCGTGGAAGCCAAGATTCTGTGCTGCAATGGATCAAAGTATTTTCTGTGGTTTG
AGATTTTCTAAGATACTCTCTCTTTACAGAATTCCCGGGCACACGAATGATTCCAGGGT
TCCTCCAGCACTTTGGTATTACTTGAAAGCAATCTTAAGGGATCTAGAATGAACCAAC
GCCCAAAAAGGATCCCTTAGCAGCGGTGATATCAAAGAAACACTTTTGAAGAACTAAT
TTTCCACCCAGATTTCCCCAATTTTAAAAGCAATGGGCAAAGCCTTCTCCACTCCTAAA
CTTCCTGGAACTGTCTTTTGGCTATATCAGGCCCCTGAAGTTAGAGTCTTTGAAAGACT
CCAAACTCCAAATTCTA
[Y]
GCTTTTATTCTCAGGCTCCTCATAATTCTACAGCACACCAGACTGCTGACCACTCTCCG
TACCACTTTTAAATTATTTCTTCCCACAGCTTTCTTAACAATGAACCTTTGAAATCTTTT
TAGTTTTCCATTTATTTTGCTACCTTTCCTCTGTCCTAGCTCTAAAATGAAGATCCTCTA
AGGTTCTACAGTTTACTTCTTGTATTCTCCTTTGTAAGTCATCTCCAAGACGATGTCCA
AATCCATCACCATTAAAATTAATAGTTTCCTCACCCACAACACTTAATATTTTAAAAAA
AATACTTTTCATTGTATTATAATTACTTGATACATACATATTTGCTCTGTGAGTTCCTTA
TTCATCATATTAGTGCCTGACAATAAATGTGTGCTGGATTGAGCTGAATCTTTATTACA
TCTCTGCTCAGTCATTTTTAATTTCTTCTTTTCTCACCACAGCCAATCAGTTGCCAATAG
ATTCTAGCCCCCAAACGTCTCTTC

LTA4H_15525 (S=C/G)
AAAAGCAATGGGCAAAGCCTTCTCCACTCCTAAACTTCCTGGAACTGTCTTTTGGCTAT
ATCAGGCCCCTGAAGTTAGAGTCTTTGAAAGACTCCAAACTCCAAATTCTATGCTTTTA
TTCTCAGGCTCCTCATAATTCTACAGCACACCAGACTGCTGACCACTCTCCGTACCACT
TTTAAATTATTTCTTCCCACAGCTTTCTTAACAATGAACCTTTGAAATCTTTTTAGTTTT
CCATTTATTTTGCTACCTTTCCTCTGTCCTAGCTCTAAAATGAAGATCCTCTAAGGTTCT
ACAGTTTACTTCTTGTATTCTCCTTTGTAAGTCATCTCCAAGACGATGTCCAAATCCAT
CACCATTAAAATTAATAGTTTCCTCACCCACAACACTTAATATTTTAAAAAAAATACTT

FIG. 6.13

TTCATTGTATTATAATTACTTGATACATACATATTTGCTCTGTGAGTTCCTTATTCATCA
TATTAGTGCCTGACAATAAATGTGT
[S]
CTGGATTGAGCTGAATCTTTATTACATCTCTGCTCAGTCATTTTTAATTTCTTCTTTTCT
CACCACAGCCAATCAGTTGCCAATAGATTCTAGCCCCCAAACGTCTCTTCTCTCAGTTA
CTCCTTTCTTTTCCACTGCCTTTGTATGACTTCAGGTCCTCATAATCTCTAGCAAGGCTG
TTGTAAAAATTAACGAGATAATGTATGGCACTTCTTAATGAAGTGCTAGGAAAAAAAT
CTAAAGTATTATTTTTGCTGATACCTTTTTTAGACGTTAAAAGGGTTTACTGATGATTT
GTGCCACCTGTTTCCAACACAAAATTCGAAACATTCTATCGTAATCACCCCTCCCTACC
TGAGCTCCTGTTTCCCACCACAGCCTATGATAACCAGGACTGCCCAGTTAGTGGGGCG
CTCTGACCACATTTGTTCCATACTCAGAACTCCCAGTAACTTCTCAACCAAACACTTCT
CGGCCTGGCTGTTTAAAGTGCTTTA

LTA4H_16561 (R=A/G)
TCTCTCCTGCTGCTCCCTGAACATCAATTAAACTGGCCTGTTTAGTGTAAGAGAAGCTG
GTAGGCAATTTTGGTGATCCAAAAGAAAGGCAACAAGAGAACATGCCATGGAACATG
CCATGGTCAGTGTCCTCACACAACTCGTGAAAGACCAGGGTTCAGGTCCGATTGAAGG
AGGGGGTTCAGTATAAAAAGCAGTATATTGAGGCCGGGCACGGTGGCTCACGCCTGTA
ATCCCAACACTCTGGGAGACAAAGGCAGGTGGATTGTTTGAGCTCAGGAGTTCGAGAC
CAGCCTGGGCAATATGGTGAAACCCTGCCTCTAGCAAAAGTACAAAAACAGCCGGGT
GTGGTAGTGCGCATCTGTGGTCCCAGCTACTTGTAAGGCTGAGGTAGGAGGATCACTT
GAGCCTGGAAGGCAGAGGGTGCAGTGAGCTAAGATCACATCACTGCACGCCAGGCTG
AGCCACAGAGTGAGACCCTGTTTCTAAAAAAAAAGAAG
[R]
AAGAAAGCAGTATATTGGAGGCAATAAGACTGCCAGGGTTTGAATCTCAACTTTTACT
ACTCACTAGCTGTGCAACCTAGGGCAAGACACTTTACCTAGCTAAACCTAACTTACCT
CCTTGGGAAATGGGGATAATAACTTATAACAGTGTTGTAATTAACATAATACTTATAA
AATATTTTTATTGCAGAAGTTTGAAGGAAGATACAATAGCTTATTGTCTAAATCCCTCA
CCATCCTTGTGCAGAAAGGAGGCACTCAATTACTTGAAGTGAAAAACCATATTTGTAA
ACTGCAGAAATTATTCTTTTGGCCTCAGGGTTAAGGCCAAAACACCTAAGAACTCTGC
TTTCATCATTTACTAGTAACAGTTTCAGGAAGGCATACTATTCTTTCAGATATTTTGAG
GCTCTCTAGGAGTTAGGAGAATGAGAAGGAAAGCATTAGCAGGCAAGTACTTACTTG
GGCTTTATGGGAGGCAGTCCAGGAGAGTAGAGCCA

LTA4H_16602 (W=A/T)
TTAGTGTAAGAGAAGCTGGTAGGCAATTTTGGTGATCCAAAAGAAAGGCAACAAGAG
AACATGCCATGGAACATGCCATGGTCAGTGTCCTCACACAACTCGTGAAAGACCAGGG
TTCAGGTCCGATTGAAGGAGGGGGTTCAGTATAAAAAGCAGTATATTGAGGCCGGGC
ACGGTGGCTCACGCCTGTAATCCCAACACTCTGGGAGACAAAGGCAGGTGGATTGTTT
GAGCTCAGGAGTTCGAGACCAGCCTGGGCAATATGGTGAAACCCTGCCTCTAGCAAAA
GTACAAAAACAGCCGGGTGTGGTAGTGCGCATCTGTGGTCCCAGCTACTTGTAAGGCT
GAGGTAGGAGGATCACTTGAGCCTGGAAGGCAGAGGGTGCAGTGAGCTAAGATCACA
TCACTGCACGCCAGGCTGAGCCACAGAGTGAGACCCTGTTTCTAAAAAAAAAGAAGG
AAGAAAGCAGTATATTGGAGGCAATAAGACTGCCAGGGTT
[W]
GAATCTCAACTTTTACTACTCACTAGCTGTGCAACCTAGGGCAAGACACTTTACCTAGC
TAAACCTAACTTACCTCCTTGGGAAATGGGGATAATAACTTATAACAGTGTTGTAATT
AACATAATACTTATAAAATATTTTTATTGCAGAAGTTTGAAGGAAGATACAATAGCTT
ATTGTCTAAATCCCTCACCATCCTTGTGCAGAAAGGAGGCACTCAATTACTTGAAGTG
AAAAACCATATTTGTAAACTGCAGAAATTATTCTTTTGGCCTCAGGGTTAAGGCCAAA
ACACCTAAGAACTCTGCTTTCATCATTTACTAGTAACAGTTTCAGGAAGGCATACTATT
CTTTCAGATATTTTGAGGCTCTCTAGGAGTTAGGAGAATGAGAAGGAAAGCATTAGCA
GGCAAGTACTTACTTGGGCTTTATGGGAGGCAGTCCAGGAGAGTAGAGCCAGGCATTC
CAATCAACTTGATTGAGAACATCAACCTATGAAT

LTA4H_16781 (K=G/T)
GAGACAAAGGCAGGTGGATTGTTTGAGCTCAGGAGTTCGAGACCAGCCTGGGCAATA
TGGTGAAACCCTGCCTCTAGCAAAAGTACAAAAACAGCCGGGTGTGGTAGTGCGCATC
TGTGGTCCCAGCTACTTGTAAGGCTGAGGTAGGAGGATCACTTGAGCCTGGAAGGCAG

FIG. 6.14

AGGGTGCAGTGAGCTAAGATCACATCACTGCACGCCAGGCTGAGCCACAGAGTGAGA
CCCTGTTTCTAAAAAAAAAGAAGGAAGAAAGCAGTATATTGGAGGCAATAAGACTGC
CAGGGTTTGAATCTCAACTTTTACTACTCACTAGCTGTGCAACCTAGGGCAAGACACTT
TACCTAGCTAAACCTAACTTACCTCCTTGGGAAATGGGGATAATAACTTATAACAGTG
TTGTAATTAACATAATACTTATAAAATATTTTTATTGCAGAAGTTTGAAGGAAGATACA
ATAGCTTATT
[K]
TCTAAATCCCTCACCATCCTTGTGCAGAAAGGAGGCACTCAATTACTTGAAGTGAAAA
ACCATATTTGTAAACTGCAGAAATTATTCTTTTGGCCTCAGGGTTAAGGCCAAAACAC
CTAAGAACTCTGCTTTCATCATTTACTAGTAACAGTTTCAGGAAGGCATACTATTCTTT
CAGATATTTTGAGGCTCTCTAGGAGTTAGGAGAATGAGAAGGAAAGCATTAGCAGGC
AAGTACTTACTTGGGCTTTATGGGAGGCAGTCCAGGAGAGTAGAGCCAGGCATTCCAA
TCAACTTGATTGAGAACATCAACCTATGAATAGTAAGAATTCACAGTTTACAATAGAA
TGCCCTTTCCTGTCAAAAAAAAATTTAAACTTGTAAGTCCTTAGATATATAATTTTGTC
TAATCTGCTATATCAAGATAATTTCTAAATCTTTTTTAAAAATTAATATTTTAAATTGAT
AGATCATAATTGTGTATACTTATGTGACACAAT

LTA4H_17144 (R=A/G)
ACCTAGCTAAACCTAACTTACCTCCTTGGGAAATGGGGATAATAACTTATAACAGTGT
TGTAATTAACATAATACTTATAAAATATTTTTATTGCAGAAGTTTGAAGGAAGATACA
ATAGCTTATTGTCTAAATCCCTCACCATCCTTGTGCAGAAAGGAGGCACTCAATTACTT
GAAGTGAAAAACCATATTTGTAAACTGCAGAAATTATTCTTTTGGCCTCAGGGTTAAG
GCCAAAACACCTAAGAACTCTGCTTTCATCATTTACTAGTAACAGTTTCAGGAAGGCA
TACTATTCTTTCAGATATTTTGAGGCTCTCTAGGAGTTAGGAGAATGAGAAGGAAAGC
ATTAGCAGGCAAGTACTTACTTGGGCTTTATGGGAGGCAGTCCAGGAGAGTAGAGCCA
GGCATTCCAATCAACTTGATTGAGAACATCAACCTATGAATAGTAAGAATTCACAGTT
TACAATAGAATGCCCTTTCCTGTC
[R]
AAAAAAAATTTAAACTTGTAAGTCCTTAGATATATAATTTTGTCTAATCTGCTATATCA
AGATAATTTCTAAATCTTTTTTAAAAATTAATATTTTAAATTGATAGATCATAATTGTG
TATACTTATGTGACACAATGCGATGTTTTGATATATGTACTCAATGTGGACTAAGTCAA
GCTAATATATCCATTACCTCATCTAACTCTATCTTCTAAAATTTATATTCATCACCATAC
TATTGATGACTTCTCTGAAATAGGAAAATTCTACAGGTAGTTCATGTGGTTAAGATCAC
ATTTAAAATAGAAAAAATATGCAATGAGAGGTTGAGTCCTAAAGTTCTGAACCAATAC
TACTATTAGATAATACAAGTTAACCTAATCAGTCAATAAATAGAGATATATCGAGCAT
GAAAAATAGAAAAGGTTTTTAAATCCAACCTTATCTTTAAAATAGGAATACAGGAAAT
CCTTCCAGTCATCAGTAGTTATGCTCTTAT

LTA4H_17754 (R=A/G)
AATTGTGTATACTTATGTGACACAATGCGATGTTTTGATATATGTACTCAATGTGGACT
AAGTCAAGCTAATATATCCATTACCTCATCTAACTCTATCTTCTAAAATTTATATTCAT
CACCATACTATTGATGACTTCTCTGAAATAGGAAAATTCTACAGGTAGTTCATGTGGTT
AAGATCACATTTAAAATAGAAAAAATATGCAATGAGAGGTTGAGTCCTAAAGTTCTGA
ACCAATACTACTATTAGATAATACAAGTTAACCTAATCAGTCAATAAATAGAGATATA
TCGAGCATGAAAAATAGAAAAGGTTTTTAAATCCAACCTTATCTTTAAAATAGGAATA
CAGGAAATCCTTCCAGTCATCAGTAGTTATGCTCTTATAGGAAAACTTCTCAACATAA
GCTTTTAAGAATCCTAGGAAAATCTCTAAGAGTAAAAAAGAAAAGAAATCAATTCATA
GAAAGGTAATTATTTGACATTTTGTGTGCGT
[R]
TTTGGCATTGTACTATTAACCACAGAGAACAGAGAACATTCAGAGAATAGGGAAATCT
ACGAGGACTTTCAGAGTGAAAGAATGTTCAAAAAAGGAGGTGGGACTTAAGTTGGGC
CTTGAAGAATATATGTAATTCAGTGGAAGGGAGAAGAGAAATTCTAATTATAGGTAAG
GGGATAACACATGAAGACACAGAAAAGGAATGCATAACCCAAGTTCTAAAAGCAATA
ACCTTCACATGACTAGAAAGGAGAAAAATAAGACTGGACAGGCAGAATGGATCCAGG
TGACAGACAGCCTTCCAAGTCAATCAACCAAGGAGAACACCTCAATGTCCATCAGTGG
GGGATGGGTACATAACTCAGCATAGCTTTATCATGAACTAGTATGATGGCATTAAAAA
GTATGAAACAGATTTATATGTACTGACACAGAAGGGTGTATGTGAAATATCGAGCAAA
ACAAAACACAAATGCAGAGCCAATATATAGCATGACCCA

FIG. 6.15

LTA4H_17836 (W=A/T)
TAACTCTATCTTCTAAAATTTATATTCATCACCATACTATTGATGACTTCTCTGAAATA
GGAAAATTCTACAGGTAGTTCATGTGGTTAAGATCACATTTAAAATAGAAAAAATATG
CAATGAGAGGTTGAGTCCTAAAGTTCTGAACCAATACTACTATTAGATAATACAAGTT
AACCTAATCAGTCAATAAATAGAGATATATCGAGCATGAAAAATAGAAAAGGTTTTTA
AATCCAACCTTATCTTTAAAATAGGAATACAGGAAATCCTTCCAGTCATCAGTAGTTAT
GCTCTTATAGGAAAACTTCTCAACATAAGCTTTTAAGAATCCTAGGAAAATCTCTAAG
AGTAAAAAAGAAAAGAAATCAATTCATAGAAAGGTAATTATTTGACATTTTGTGTGCG
TGTTTGGCATTGTACTATTAACCACAGAGAACAGAGAACATTCAGAGAATAGGGAAAT
CTACGAGGACTTTCAGAGTGAAAGA
[W]
TGTTCAAAAAAGGAGGTGGGACTTAAGTTGGGCCTTGAAGAATATATGTAATTCAGTG
GAAGGGAGAAGAGAAATTCTAATTATAGGTAAGGGGATAACACATGAAGACACAGAA
AAGGAATGCATAACCCAAGTTCTAAAAGCAATAACCTTCACATGACTAGAAAGGAGA
AAAATAAGACTGGACAGGCAGAATGGATCCAGGTGACAGACAGCCTTCCAAGTCAAT
CAACCAAGGAGAACACCTCAATGTCCATCAGTGGGGGATGGGTACATAACTCAGCAT
AGCTTTATCATGAACTAGTATGATGGCATTAAAAAGTATGAAACAGATTTATATGTAC
TGACACAGAAGGGTGTATGTGAAATATCGAGCAAAACAAAACACAAATGCAGAGCCA
ATATATAGCATGACCCATTTTTTGTAATTAAAATAATTACATGTATTTATTTGTCTGCTT
GTTAATTTACACCTAGAAAATGATCTGGAGCCATTTACA

LTA4H_17863 (R=A/G)
CCATACTATTGATGACTTCTCTGAAATAGGAAAATTCTACAGGTAGTTCATGTGGTTAA
GATCACATTTAAAATAGAAAAAATATGCAATGAGAGGTTGAGTCCTAAAGTTCTGAAC
CAATACTACTATTAGATAATACAAGTTAACCTAATCAGTCAATAAATAGAGATATATC
GAGCATGAAAAATAGAAAAGGTTTTTAAATCCAACCTTATCTTTAAAATAGGAATACA
GGAAATCCTTCCAGTCATCAGTAGTTATGCTCTTATAGGAAAACTTCTCAACATAAGCT
TTTAAGAATCCTAGGAAAATCTCTAAGAGTAAAAAAGAAAAGAAATCAATTCATAGA
AAGGTAATTATTTGACATTTTGTGTGCGTGTTTGGCATTGTACTATTAACCACAGAGAA
CAGAGAACATTCAGAGAATAGGGAAATCTACGAGGACTTTCAGAGTGAAAGAATGTT
CAAAAAAGGAGGTGGGACTTAA
[R]
TTGGGCCTTGAAGAATATATGTAATTCAGTGGAAGGGAGAAGAGAAATTCTAATTATA
GGTAAGGGGATAACACATGAAGACACAGAAAAGGAATGCATAACCCAAGTTCTAAAA
GCAATAACCTTCACATGACTAGAAAGGAGAAAAATAAGACTGGACAGGCAGAATGGA
TCCAGGTGACAGACAGCCTTCCAAGTCAATCAACCAAGGAGAACACCTCAATGTCCAT
CAGTGGGGGATGGGTACATAACTCAGCATAGCTTTATCATGAACTAGTATGATGGCAT
TAAAAAGTATGAAACAGATTTATATGTACTGACACAGAAGGGTGTATGTGAAATATCG
AGCAAAACAAAACACAAATGCAGAGCCAATATATAGCATGACCCATTTTTTGTAATTA
AAATAATTACATGTATTTATTTGTCTGCTTGTTAATTTACACCTAGAAAATGATCTGGA
GCCATTTACACCAAACTGCTAACAGTGGTTACCCCTG

LTA4H_19259 / SG12S25 (R=A/G)
GTCTATATCTGTCAGATCAACCACAAGTTTGGTGAAAGGATGTGTCTCCCCAAATGTCT
TTACCTGCAAGACATGAAATAACATGGAGAAACATATAGAAAGACTGCTATCACCAC
GCAAATAAGCTAATAAGGAGGTATTACTTCACTCAGTGGTGTAACTTTAGGGGAATCT
AAAACTTGGAGACTGGAACACTAGGATATGTTGGCATAAACTTCTGGAAGTCTATTAA
TAGAATGCTTACTTAAGTAATATTCTCTGTTGTTTCTTGCTCAATAATACAGGCTTTATT
CTTATAAAAAGACTAGAAAAATGATTTAATGCCTGGTCAGCAAATTTGGCTTTCAGGA
GACAACACTTAAAAATGACATACCAAATAAGATGCAAACATAGTAAACAGCTATATT
AATAGCAAAGACCCAGTGAGGTCCCACAGCTCCCTATTTAGACCAGGTCATCAAAACT
ACCTTACATAGAACAGTGAAC
[R]
GTGTGGATCAACACAGTGTTATACCAGCATTGACTTCACTTTCCACACTTGTAAAAATG
ACTTTTTGGTTGCTACACAGTAAAGACGCTTTTATAAAAACTCAGTTTTTAACACCTAT
ACAACTTTGGATGAAGGTTTTTAAAACTTTGACTCCTTTACCGAATTCTGTAGTTCTCC
CCATCCTCCCAGAGCATTAAAATGTCTGAACTTTTCACCAAACAATCGTCCGCAAATGT
GGCGTTCCAAGTACACAGTATGTCCCTCATTTAACCTGAAAAAAAAATATTTTAATAA
AAACACGGACACAGCTGAGAAGAAAAGACATTTCAATCAAGATATTTTCTTTTTGGCT

FIG. 6.16

TTTCTACAGAGGAAAGCAGTTGTAAGGCATGACCACTACAGTCTAAGCCGACTCTGGC
TCCCAGGCAGTCAATCCAGAGCAATGGGAAGCCCAGCCCAGCAGATGGCAGCAGGGA
AAGTTAAGCCCTGCTTCTGCT

LTA4H_19371 (Y=C/T)
TATCACCACGCAAATAAGCTAATAAGGAGGTATTACTTCACTCAGTGGTGTAACTTTA
GGGGAATCTAAAACTTGGAGACTGGAACACTAGGATATGTTGGCATAAACTTCTGGAA
GTCTATTAATAGAATGCTTACTTAAGTAATATTCTCTGTTGTTTCTTGCTCAATAATACA
GGCTTTATTCTTATAAAAAGACTAGAAAAATGATTTAATGCCTGGTCAGCAAATTTGG
CTTTCAGGAGACAACACTTAAAAATGACATACCAAATAAGATGCAAACATAGTAAAC
AGCTATATTAATAGCAAAGACCCAGTGAGGTCCCACAGCTCCCTATTTAGACCAGGTC
ATCAAAACTACCTTACATAGAACAGTGAACAGTGTGGATCAACACAGTGTTATACCAG
CATTGACTTCACTTTCCACACTTGTAAAAATGACTTTTTGGTTGCTACACAGTAAAGAC
GCTTTTATAAAAACTCAGTTTTTAA
[Y]
ACCTATACAACTTTGGATGAAGGTTTTTAAAACTTTGACTCCTTTACCGAATTCTGTAG
TTCTCCCCATCCTCCCAGAGCATTAAAATGTCTGAACTTTTCACCAAACAATCGTCCGC
AAATGTGGCGTTCCAAGTACACAGTATGTCCCTCATTTAACCTGAAAAAAAAATATTT
TAATAAAAACACGGACACAGCTGAGAAGAAAAGACATTTCAATCAAGATATTTTCTTT
TTGGCTTTTCTACAGAGGAAAGCAGTTGTAAGGCATGACCACTACAGTCTAAGCCGAC
TCTGGCTCCCAGGCAGTCAATCCAGAGCAATGGGAAGCCCAGCCCAGCAGATGGCAG
CAGGGAAAGTTAAGCCCTGCTTCTGCTCTTGCATGTCCCTATGTTAAAAGTGGGAGTAT
ATCAGGAATTAAACTTAACACCTAGACTGAACCTAACACTCCTAACGCTGTAATAAGT
GTTACAGAATTTTTAAGAA

LTA4H_21886 (W=A/T)
AACTTACATTGGAGAGTGACTTGTCGCCTGCCTACAAAAAAAGAAAATTACCTTAGTA
TTTTAGTAATCGAATTACAGACTATCTAAAAGACTGCCTACCTAAATACTTAGCATACT
GGCACTGGTGATCCACTGTATTTCTACTACAGCACTTCAAAGAAGGTAAAAGAGACCT
TAATTGAAAAAACAAAAAAAATACAGAACTAAAAATTAGCATCATTCTTTCTTGCCCT
AATTCTAGGGAATTTTTGCAATACAATGAAAGCCAGTCTATTTGTGTCTAACTTCCATG
AAACATTTCTTCTACTTCCATTTTTATATCTGCTCTTATTTACCCATCACTTTCTTTCTCT
CCTATTACCCAAAATATATTTAATAAAACTTTAGAGTGTCCTATGTGTCCTGTGCTGTA
TTTTATTTATTTTATTGCTAATCCATCACTCATTTTGGTTCTAAGAAGAATTTAAAGTAG
CTCACAGGCATATTAAACATAGCAGCGT
[W]
CTATGGCCCTAATCCTTTCCTGTACATGGTGTACTGATTTTTTTTTTAATTGTACCTACA
CACCAAGTGTAATTGGTATAGTCTGATTGTCTGGATACATAATTTATCAATGAATTGTT
GTTACACAGCACCCCCATGCCCAACTCCCCAAATACCGTGAACATAATATTCTCCTTCT
CCAAATGGCCTGATTATTTTCCTTTCAAAAACAAGATGGAGGCCTGGTGGGGTGGTTC
ATGCCTGTAATCCCAGCACTTTGGGAGGCCAAGGCAGGTGGATCACGAGGTCAGAGG
ATCGAGACTACCCTGGCCAATATAGTGAAACCCCATCTCTACTAAAATTACAAAAATT
AGCTGGGCATGGTGGTGTGCACCTATAGTCCCAGCTACTCAAGAGGCTGAGGCAGGAG
AATCGCTTGAACCCGGGGGCAGAGGTTGCAGTGAGCTGAGATTGTGCCACTGCACTCC
AACCTGGGCAACAG

LTA4H_23826 (R=A/G)
GTTTATTGCCTCTTGTAAGACCTCTTGAGGGTCTCATTTCATCCCTCAATTTCACAACTA
TAGAAACCCAGTCACAACTCATAAGAAACTATTTTTTTTTTTTTTTTTTTTTTTTTGAGAC
GGAGTCTCGCTCTGTCACCCAGGCTGGAGTGCAGTGGCACGATCTTGGCTCACTGCAA
GCTCCACCTCCCAGGTTCACACCATTCTCCTGCCTCAGCCTCCCTAGTAGCTGGGACTA
CAGGTGCCCGCCACCACGCCCAGCTAATTTTTTCTTTTTTTTGTATTTTTAGTAGAGACA
GGGTTTCACTGTGTTAGCCAGGATGGTCTCAATTCCCTGACCTCATGATCCGCCTGCCT
CGGCCACCCAAATTGCTGGGATTACAGGCGTGAGCCACCACGCCCAGCGTTTTTTTTT
TTTTTTTTTTAAATATACAGGGTCTCATTCTGTTGCCCAGGCTGAGTACAGAGGGGCCA
TCACAGCTCACTGCAGCCTCC
[R]
CCTCCTGGGCTCAAGCAATACTCCCACCTCAGCCTTCTGAGTAGCTGGGACTACAGGC
ATACACTACCATGCCCGATTAATTTTTATTTTTTGTAGAGACATGATCTCACTTATGT

FIG. 6.17

TGCCCGGCCTGGTCTTGAACTCCTGGGCTCAAGCGATCCTCCCACTTTGGCCTCCCAAA
GTGACGGGATTACAGGCATGAGCCACAGAGCCCAGCCTGTAAGACTATTCTAGAACA
GGAATGGGTATAAACTTTGTCATGCACTTAAAGGTTGAATACTCTTATATAAGAAGAA
ACAAATAGAAAATGAAGGAAATCCTGTCAGATGCTATAACGTGGATAAACCTTAAGG
GCATTATGACACCTTGAATGAAATAAGCCAGACACAAAGAGATAAAATCATACTGTAT
GATTCTACTTATGTGAGGTATCTAAAGTAATCAAATTCATAGGAACAGAAAATAGAAT
GGGTGTTACCAAGGACT

LTA4H_24035 (Y=C/T)
CTCCCTAGTAGCTGGGACTACAGGTGCCCGCCACCACGCCCAGCTAATTTTTTCTTTTT
TTTGTATTTTTAGTAGAGACAGGGTTTCACTGTGTTAGCCAGGATGGTCTCAATTCCCT
GACCTCATGATCCGCCTGCCTCGGCCACCCAAATTGCTGGGATTACAGGCGTGAGCCA
CCACGCCCAGCGTTTTTTTTTTTTTTTTTTTTAAATATACAGGGTCTCATTCTGTTGCCC
AGGCTGAGTACAGAGGGGCCATCACAGCTCACTGCAGCCTCCACCTCCTGGGCTCAAG
CAATACTCCCACCTCAGCCTTCTGAGTAGCTGGGACTACAGGCATACACTACCATGCC
CGATTAATTTTTTATTTTTTTGTAGAGACATGATCTCACTTATGTTGCCCGGCCTGGTCT
TGAACTCCTGGGCTCAAGCGATCCTCCCACTTTGGCCTCCCAAAGTGACGGGATTACA
GGCATGAGCCACAGAGC
[Y]
CAGCCTGTAAGACTATTCTAGAACAGGAATGGGTATAAACTTTGTCATGCACTTAAAG
GTTGAATACTCTTATATAAGAAGAAACAAATAGAAAATGAAGGAAATCCTGTCAGAT
GCTATAACGTGGATAAACCTTAAGGGCATTATGACACCTTGAATGAAATAAGCCAGAC
ACAAAGAGATAAAATCATACTGTATGATTCTACTTATGTGAGGTATCTAAAGTAATCA
AATTCATAGGAACAGAAAATAGAATGGGTGTTACCAAGGACTGGGCGGTGGGGGAAA
GAGGAGCTATTGTTTAATTGGTGCAGAGTTTCAGTTCTGCAAAATGAAAAATTTCTGA
AGATCTGTTTCACAACAATGTGGATATACTTAACACTACTGAACCGCACACTTAAAAA
CAGTTAAGTGTGCTTAAAACTAAGAATGAACAAAAAATTAAGAAGGAAGGGCACTTT
ATTTGTAAAATATTGATAAAAT

LTA4H_24042 (R=A/G)
AGTAGCTGGGACTACAGGTGCCCGCCACCACGCCCAGCTAATTTTTTCTTTTTTTTGTA
TTTTTAGTAGAGACAGGGTTTCACTGTGTTAGCCAGGATGGTCTCAATTCCCTGACCTC
ATGATCCGCCTGCCTCGGCCACCCAAATTGCTGGGATTACAGGCGTGAGCCACCACGC
CCAGCGTTTTTTTTTTTTTTTTTTTTAAATATACAGGGTCTCATTCTGTTGCCCAGGCTG
AGTACAGAGGGGCCATCACAGCTCACTGCAGCCTCCACCTCCTGGGCTCAAGCAATAC
TCCCACCTCAGCCTTCTGAGTAGCTGGGACTACAGGCATACACTACCATGCCCGATTA
ATTTTTTATTTTTTTGTAGAGACATGATCTCACTTATGTTGCCCGGCCTGGTCTTGAACT
CCTGGGCTCAAGCGATCCTCCCACTTTGGCCTCCCAAAGTGACGGGATTACAGGCATG
AGCCACAGAGCCCAGCCT
[R]
TAAGACTATTCTAGAACAGGAATGGGTATAAACTTTGTCATGCACTTAAAGGTTGAAT
ACTCTTATATAAGAAGAAACAAATAGAAAATGAAGGAAATCCTGTCAGATGCTATAA
CGTGGATAAACCTTAAGGGCATTATGACACCTTGAATGAAATAAGCCAGACACAAAG
AGATAAAATCATACTGTATGATTCTACTTATGTGAGGTATCTAAAGTAATCAAATTCAT
AGGAACAGAAAATAGAATGGGTGTTACCAAGGACTGGGCGGTGGGGGAAAGAGGAG
CTATTGTTTAATTGGTGCAGAGTTTCAGTTCTGCAAAATGAAAAATTTCTGAAGATCTG
TTTCACAACAATGTGGATATACTTAACACTACTGAACCGCACACTTAAAAACAGTTAA
GTGTGCTTAAAACTAAGAATGAACAAAAAATTAAGAAGGAAGGGCACTTTATTTGTAA
AATATTGATAAAATATCTTACAT

LTA4H_24395 (R=A/G)
ATTTTTTTGTAGAGACATGATCTCACTTATGTTGCCCGGCCTGGTCTTGAACTCCTGGG
CTCAAGCGATCCTCCCACTTTGGCCTCCCAAAGTGACGGGATTACAGGCATGAGCCAC
AGAGCCCAGCCTGTAAGACTATTCTAGAACAGGAATGGGTATAAACTTTGTCATGCAC
TTAAAGGTTGAATACTCTTATATAAGAAGAAACAAATAGAAAATGAAGGAAATCCTGT
CAGATGCTATAACGTGGATAAACCTTAAGGGCATTATGACACCTTGAATGAAATAAGC
CAGACACAAAGAGATAAAATCATACTGTATGATTCTACTTATGTGAGGTATCTAAAGT
AATCAAATTCATAGGAACAGAAAATAGAATGGGTGTTACCAAGGACTGGGCGGTGGG

FIG. 6.18

GGAAAGAGGAGCTATTGTTTAATTGGTGCAGAGTTTCAGTTCTGCAAAATGAAAAATT
TCTGAAGATCTGTTTCAC
[R]
ACAATGTGGATATACTTAACACTACTGAACCGCACACTTAAAAACAGTTAAGTGTGCT
TAAAACTAAGAATGAACAAAAAATTAAGAAGGAAGGGCACTTTATTTGTAAAATATT
GATAAAATATCTTACATTTCTGTAATATTTGTAGGCTTCCAAGTTCTTTAATATATTTTA
TCTCATTTGTTTCACATAACCACCCTATGAGGTAGAAAGTCAGACATTATAATTTCAAG
GATAAGGAAACAGAGATTGAGAGTGACTTGTTCAAGCTTACATGAGAATCCAGATCTC
TAAAGGTAAGAGCATGCTCATTTTACAATACTTGAAAAAATAAGGGGTAACTGGTCAA
GATTTTTAAATGTAAAATTAATTTGTTGCCTACATTTTAGATTTGAATTTTTCTAGAGCT
GTCAGCTTGATATCTTGAGAAATATGCAAATGATTGACCAATTAACCTTGAGAGAAGT
TCAAGATGCCTAAGTTTTGATCTTTCCACAAA

LTA4H_24509 / SG12S26 (Y=C/T)
ACAGAGCCCAGCCTGTAAGACTATTCTAGAACAGGAATGGGTATAAACTTTGTCATGC
ACTTAAAGGTTGAATACTCTTATATAAGAAGAAACAAATAGAAAATGAAGGAAATCC
TGTCAGATGCTATAACGTGGATAAACCTTAAGGGCATTATGACACCTTGAATGAAATA
AGCCAGACACAAAGAGATAAAATCATACTGTATGATTCTACTTATGTGAGGTATCTAA
AGTAATCAAATTCATAGGAACAGAAAATAGAATGGGTGTTACCAAGGACTGGGCGGT
GGGGGAAAGAGGAGCTATTGTTTAATTGGTGCAGAGTTTCAGTTCTGCAAAATGAAAA
ATTTCTGAAGATCTGTTTCACAACAATGTGGATATACTTAACACTACTGAACCGCACAC
TTAAAAACAGTTAAGTGTGCTTAAAACTAAGAATGAACAAAAAATTAAGAAGGAAGG
GCACTTTATTTGTAAAATA
[Y]
TGATAAAATATCTTACATTTCTGTAATATTTGTAGGCTTCCAAGTTCTTTAATATATTTT
ATCTCATTTGTTTCACATAACCACCCTATGAGGTAGAAAGTCAGACATTATAATTTCAA
GGATAAGGAAACAGAGATTGAGAGTGACTTGTTCAAGCTTACATGAGAATCCAGATCT
CTAAAGGTAAGAGCATGCTCATTTTACAATACTTGAAAAAATAAGGGGTAACTGGTCA
AGATTTTTAAATGTAAAATTAATTTGTTGCCTACATTTTAGATTTGAATTTTTCTAGAGC
TGTCAGCTTGATATCTTGAGAAATATGCAAATGATTGACCAATTAACCTTGAGAGAAG
TTCAAGATGCCTAAGTTTTGATCTTTCCACAAACCTGAAAATTTTTCCAAAAGCTCACC
TGCTTTCTAAAGCTCCAACAACTAAAGCAATCAGGTAGCAGGGTATTGGAACCTAAAG
AGGGCAAACAAACGCACACCACGTGCTT

LTA4H_25034 (R=A/G)
GTAGGCTTCCAAGTTCTTTAATATATTTTATCTCATTTGTTTCACATAACCACCCTATGA
GGTAGAAAGTCAGACATTATAATTTCAAGGATAAGGAAACAGAGATTGAGAGTGACT
TGTTCAAGCTTACATGAGAATCCAGATCTCTAAAGGTAAGAGCATGCTCATTTTACAA
TACTTGAAAAAATAAGGGGTAACTGGTCAAGATTTTTAAATGTAAAATTAATTTGTTG
CCTACATTTTAGATTTGAATTTTTCTAGAGCTGTCAGCTTGATATCTTGAGAAATATGC
AAATGATTGACCAATTAACCTTGAGAGAAGTTCAAGATGCCTAAGTTTTGATCTTTCCA
CAAACCTGAAAATTTTTCCAAAAGCTCACCTGCTTTCTAAAGCTCCAACAACTAAAGC
AATCAGGTAGCAGGGTATTGGAACCTAAAGAGGGCAAACAAACGCACACCACGTGCT
TGCATTAGTGTTCACAAATGTTACACA
[R]
TAAGACAATTCATATTTAAAAGTAAGTAAATTCCCTTTCAAATCTCCTAATATTAGTAG
GGATAACTTTGCTTTTATACTTCTCAAATAGTTCTCATCTTTAACATATAGCTTAAAATT
GTGATATAAAACATTGTTCAAAACATCTATTTGCCTTTTATTCTGCTAGGAACAAAAGC
TTCTCACACATGAAAAACAAGATCACACATACTATTAAAAGGTGCATTTTGAGCATTT
CTCAAAAAGTAACCTACAGGAAGCGCATTTCCCATATGTTTGCCTTTTTCCTCCTGACT
TTTAAAAGGTTTTGGTTTTCTTTTTTTATTCCTTTATGTTTCAAAGCACTATTGGCATGT
TGTAGAGGCACACAGAGTTACCCGGCAATAAGTAGATGCCAAAGTTATGGGAGCTTG
GAACCACAGAAGCTGCAGTGGAAGTCAAATTATCCATTGTGAGGTCAATTAAGAAAA
CACACACACACACACACACACACACACAC

LTA4H_26441 (Y=C/T)
ACCGCCAATGAAAACAAAAATCTAGACCCTAGGATCTTACTTTTTGGATGAATTTGTA
TATTTTCCTGCTTGGGTCTTCTGGGTCAGGTGTTTCTCCATCACGAATAGCACTCATAA
GTGCCACCAGTTCTTTAGGGACAGACACCTAATCAAGGAGAAAAATCATTTCTAGTCA

FIG. 6.19

TAAATAAAAGCTTCTATGTGTCTTAAACCATATATGTAAAATAACCTTTTCTTCCCATT
CTTGACTATCTAATAAACAGACTATGAACACAAAAAGTATATACATATACAAAAAGTA
TATATATACACACACATATATATGAACACAACGTGTATAGATGTGTATATATATGCAC
ACATATATATGTGTATATATATAAAACACATATACAAAAAGTATATATATACACATAT
ACATATCAGTTTTGTAAATAAAATTAGCAATATGGGAAACTGGCTTCTTTAAAAGTGA
ATGTGAAATTTCTATCCATTCACCCATGCACA
[Y]
TAAGAGCAGAGTTTTGGTAGAAACTGGATTAAAATCCCAGCTCTGCCACCTAATAACT
AACTGCACAAACTTGGGCAAATAAATATAACCCCCGAGCCTCAGTTTCCCCATCAAGT
AAGTGTAAAACTTCAAAGGCTTGCTGCAAGGAATAAATAATATAAGTGAAGAGCCCA
GCACCATCCCTGGCAATGGCAGCCACCATCCCTGCTCCCGCTACACTCACAAAACAGA
TTCAAAAGGACGTTATATACTCACTGTAGGACAGAATGGTTTTGAACAATTTTGTTTTG
AAAACACACACTTGGAGTTACAAATAGAGGAACATTTTAAAAGTAGTAACTGTGAAA
AACTAAAATTTATTGCTAAAAACTGTCAAATAATTTTCTCTGGAAATCCATACGGAAA
AGACCCTTATGCGGCAAACCATATAGTCATTTAACTGTGTATCCTAGCTCCATGATTCT
GAAAGTTTGATTTCTGATGAATGCCAGAATAAAGGA

LTA4H_26766 (Y=C/T)
TATATATATGCACACATATATATGTGTATATATATAAAACACATATACAAAAAGTATA
TATATACACATATACATATCAGTTTTGTAAATAAAATTAGCAATATGGGAAACTGGCT
TCTTTAAAAGTGAATGTGAAATTTCTATCCATTCACCCATGCACATTAAGAGCAGAGTT
TTGGTAGAAACTGGATTAAAATCCCAGCTCTGCCACCTAATAACTAACTGCACAAACT
TGGGCAAATAAATATAACCCCCGAGCCTCAGTTTCCCCATCAAGTAAGTGTAAAACTT
CAAAGGCTTGCTGCAAGGAATAAATAATATAAGTGAAGAGCCCAGCACCATCCCTGG
CAATGGCAGCCACCATCCCTGCTCCCGCTACACTCACAAAACAGATTCAAAAGGACGT
TATATACTCACTGTAGGACAGAATGGTTTTGAACAATTTTGTTTTGAAAACACACACTT
GGAGTTACAAATAGAGGAACA
[Y]
TTTAAAAGTAGTAACTGTGAAAAACTAAAATTTATTGCTAAAAACTGTCAAATAATTT
TCTCTGGAAATCCATACGGAAAAGACCCTTATGCGGCAAACCATATAGTCATTTAACT
GTGTATCCTAGCTCCATGATTCTGAAAGTTTGATTTCTGATGAATGCCAGAATAAAGG
ACTCCCCCAAGTATTAATGATCAAACAAGAATATATTCCAGTAGGGGCTAGACTTTCA
TGTTCTTCTTGCATGGCTCAGGACCCAAAGCTGTGACTGAGGCAGGCACAGAATTAGA
AGTTCCTGAACCAGTGCTACAACAATTGTAGATTCTAAAGCACAAAACTATTCAGGAA
ATAATTCGGTTCAGCCACCTCCCTTCATTTAGGTGGTGATACGTTATATATATGTGCCA
GCTGAGGTTGCGAGGTCATAAAACTTGTTCAAGTGTCACATCATTATTTATTTATTTTT
TTAGAAATGGGGTCTCGCTATGTCGCCC

LTA4H_27257 (R=A/G)
CATTTTAAAAGTAGTAACTGTGAAAAACTAAAATTTATTGCTAAAAACTGTCAAATAA
TTTTCTCTGGAAATCCATACGGAAAAGACCCTTATGCGGCAAACCATATAGTCATTTA
ACTGTGTATCCTAGCTCCATGATTCTGAAAGTTTGATTTCTGATGAATGCCAGAATAAA
GGACTCCCCCAAGTATTAATGATCAAACAAGAATATATTCCAGTAGGGGCTAGACTTT
CATGTTCTTCTTGCATGGCTCAGGACCCAAAGCTGTGACTGAGGCAGGCACAGAATTA
GAAGTTCCTGAACCAGTGCTACAACAATTGTAGATTCTAAAGCACAAAACTATTCAGG
AAATAATTCGGTTCAGCCACCTCCCTTCATTTAGGTGGTGATACGTTATATATATGTGC
CAGCTGAGGTTGCGAGGTCATAAAACTTGTTCAAGTGTCACATCATTATTTATTTATTT
TTTTAGAAATGGGGTCTCGCTATGTC
[R]
CCCAGGCTGGCCTTGAACTTCTGAGTTCAAGTGATCTTCCCACCTCAGCCTCCCAAGTA
GTTGGGACTTCACGCAGTTATTAAGTGGTGGAGAAGAGCCAGAGCCCTGGGATTCTTT
GCCTCCAAGTATAATATATCACTGCACTATCCTAGATGTAATTTGGTTGTGGGATGATT
TGGGAAGCAAGAAGGCCCCATAAATATGGGTTGGTCCTCATTCTATTTGCTTGGTCTA
AGTAGGTCTAGCCTCCGGGATAGTGATTATTTAGTAATTACAGTCCGCCTTTTCCAAAA
AGGATTAGCAGTACCTACCAAGGGAATAAGTTGGAATTGCATACAGACAAGTCTGGA
ATATATGCCCACTAGGCTTATATGGCTACAGAATGCATTTATAGAAACTTAAATCATG
CAAATGTCAATTTTTTAAAAGTTAAGTAAAAATTGTTCCTAAGTTCTTATTTCTAGATCC
AGGATTCTGAATTTCTTCTTTTTGTTT

FIG. 6.20

LTA4H_27958 (Y=C/T)
TATGGGTTGGTCCTCATTCTATTTGCTTGGTCTAAGTAGGTCTAGCCTCCGGGATAGTG
ATTATTTAGTAATTACAGTCCGCCTTTTCCAAAAAGGATTAGCAGTACCTACCAAGGG
AATAAGTTGGAATTGCATACAGACAAGTCTGGAATATATGCCCACTAGGCTTATATGG
CTACAGAATGCATTTATAGAAACTTAAATCATGCAAATGTCAATTTTTAAAAGTTAAG
TAAAAATTGTTCCTAAGTTCTTATTTCTAGATCCAGGATTCTGAATTTCTTCTTTTTGTT
TGTTTGTTTTTTTGTTTTTTGGGTTTTTTTTTTGAGACGGAGTCTGGCTCTGTCGCCCAG
GCTGGAGTGCAGTGGTGCCATCTCAGCTCACTCCAAGCTCTGCCTCCTGGGTTCATGCC
ATTCTCCTGCCTCAGCCTGCCGAGTAGCTGGGACTACAGGTGCCCGCCACCATGCCCG
GCTAATTTTTTGTGTTTTTTTTAGTACAGA
[Y]
GGGGTTTCACCATGTTAGCCAGGATGGTCTCGATCTCCTGACCTCGTGATCCACCCATC
TCGGCCTCCCAAAGTGCTGGGATTACAGGTGTGAGCCACCACACCTAGCCCTGAATTC
CTTTTTAAAAGTCAGATTGGTTTCCATTTCCTTTTTTTCACAGTTAAAATGTTTAAAACT
GCCTTTAAAGTAGAGATTCAGAATGAGTGCCACAGCCTCTTTGTTTACATATTTCAGGT
AGAATTTCATTAAGAAAAATAATTCTAGCTCTAGGAATTCAATTATCATCTCTGCTTAT
CATTTATACCATATTTACTGATATGCATCATTTAATTGAGTTAATAATTCGTAATATTTA
CCTCTGCAGTATAGGTTAATTTCACAGAAGGAGTGTCCTGACAAGGAAGGATTGCTCT
GCAGTGGATGGCCTGAAAAAGGGAGAAACAAGAAGAAATAGCTATTTATCTTTCGCA
TAAGTCATTAAGAAATCATTAAAAAT

LTA4H_29353 (Y=C/T)
AATCTATGGTTAACCCTCACATTTCAGTTGAAGCATGGAGAAACTCTTAAGCAGTGTTT
CCTACTCTATGGTCTGGGTGACAGTAGTGCCCAGTGAGAAGCTTTTAGAAACCTGAGA
AAAAAGGGCTCTGTAGCAAAACAGACCTGAGAAGTATGGCATACTGCACCACTGTCTT
GCAGAGCCACTAGAATATTAGCCGCCTGAAGGCTCTGAACAGACCTACAATAAAGAA
ACCTGTTTGATTTCTTACATTTATGTTAACACAAAACCCATTTCTCTCTGGTTTAACACC
TAATGGGATGTCAGTATTCTAATGAACACAGCCTGAGAAATGTTGCTGTAATCCTGAC
ACTTCAATCTTGCAGCAAACCTTGTAAGTAAAACAAAGAAGCAAAGAAGGGAGAAAG
AACAGTCTCTTTCAATACCATCTAGACATATTCATTCATATCATATGCAAAGTGTTTCT
GTACTGCCACACCAATCGT
[Y]
ATTAACATTGGTTCCATCCAGTATGACCACAGGCCAGGTGCCGTGGCTCACTCCTGCA
ATCCCAGCACTTTGGGAGGCTCAGATGAGAGGATTGCTTGAGCTCTAGAATTTGAGAC
CAGCCTGGGCAACATAGTGAGACCTTACCTCTACACAAAAAAAATTAGCTGGGCATGG
TGGTGCACACCTGTAGTCCCAGCTACTCAGGAGGCTGAGGTAAAAGGATCGCTTGAGC
CCAGGAGTTCTAGGCTGCAGTGACCCAAGTTCGCACCATTGCACTACAGCCTGGGCAA
CACAGCAAGACCCTGTCTCCAAAAAAAAAAAAAAAAAGAGCACCTACAATCTTATACC
CGGTCTGTTTACAAATAAGTCTGTCTACTGCTGGTGAACAATGAAATGAAAACCCAGC
CTCATTGAGACAGTCTACTAAACTCAAAGGAATTCTGATATTAACACCCTTCTCTGAAG
CTATTACAAAT

LTA4H_29513 (R=A/G)
TGCACCACTGTCTTGCAGAGCCACTAGAATATTAGCCGCCTGAAGGCTCTGAACAGAC
CTACAATAAAGAAACCTGTTTGATTTCTTACATTTATGTTAACACAAAACCCATTTCTC
TCTGGTTTAACACCTAATGGGATGTCAGTATTCTAATGAACACAGCCTGAGAAATGTT
GCTGTAATCCTGACACTTCAATCTTGCAGCAAACCTTGTAAGTAAAACAAAGAAGCAA
AGAAGGGAGAAAGAACAGTCTCTTTCAATACCATCTAGACATATTCATTCATATCATA
TGCAAAGTGTTTCTGTACTGCCACACCAATCGTTATTAACATTGGTTCCATCCAGTATG
ACCACAGGCCAGGTGCCGTGGCTCACTCCTGCAATCCCAGCACTTTGGGAGGCTCAGA
TGAGAGGATTGCTTGAGCTCTAGAATTTGAGACCAGCCTGGGCAACATAGTGAGACCT
TACCTCTACACAAAAAAA
[R]
TTAGCTGGGCATGGTGGTGCACACCTGTAGTCCCAGCTACTCAGGAGGCTGAGGTAAA
AGGATCGCTTGAGCCCAGGAGTTCTAGGCTGCAGTGACCCAAGTTCGCACCATTGCAC
TACAGCCTGGGCAACACAGCAAGACCCTGTCTCCAAAAAAAAAAAAAAAAAGAGCACC
TACAATCTTATACCCGGTCTGTTTACAAATAAGTCTGTCTACTGCTGGTGAACAATGAA
ATGAAAACCCAGCCTCATTGAGACAGTCTACTAAACTCAAAGGAATTCTGATATTAAC
ACCCTTCTCTGAAGCTATTACAAATCCTAAACATACTTCATTCCACCACAAGCTTTCTT

FIG. 6.21

AAAACCCCCAAACTCCAGGTCTTTTCATTTCAGTTCTAGAAAATTCTCCAAAGATATAG
GCTCCCAAATGACCTCTAGATGGATTAAGTAGGACTAGCAGAGCCACCTGGTTCTCTC
TCCCAAAATAGATT

LTA4H_29999 (R=A/G)
TGGGCATGGTGGTGCACACCTGTAGTCCCAGCTACTCAGGAGGCTGAGGTAAAAGGAT
CGCTTGAGCCCAGGAGTTCTAGGCTGCAGTGACCCAAGTTCGCACCATTGCACTACAG
CCTGGGCAACACAGCAAGACCCTGTCTCCAAAAAAAAAAAAAAAAGAGCACCTACAA
TCTTATACCCGGTCTGTTTACAAATAAGTCTGTCTACTGCTGGTGAACAATGAAATGAA
AACCCAGCCTCATTGAGACAGTCTACTAAACTCAAAGGAATTCTGATATTAACACCCT
TCTCTGAAGCTATTACAAATCCTAAACATACTTCATTCCACCACAAGCTTTCTTAAAAC
CCCCAAACTCCAGGTCTTTTCATTTCAGTTCTAGAAAATTCTCCAAAGATATAGGCTCC
CAAATGACCTCTAGATGGATTAAGTAGGACTAGCAGAGCCACCTGGTTCTCTCTCCCA
AAATAGATTTCCAA
[R]
ACCATGCCTCTATAGTTCCTTAATGGTTTCTAGTTAGGTGACATGGCAACACCAAAGG
GGTTTTTAAATGTATTTCATTGGATAAGGCCAAACCCAGGCAAATATGCATACAGAAC
AACCGTAAGCAAATTCATCAAACAAAATCATGTCTACATGATTCCTATCACCTCAATC
ATTTATTAATTTAGCTGAAATCTGTTTCCCATATTCCCACCATTGCTGCCAATAAGAAA
TGGAATAATATATTCAAAATTAACATTTTCATGACTCATAAATCTTGCATTTCTTGCCA
ACTTTGGTTAATAGACATTCTATTAAGACATACTGCCTGAAAATCAGATATTTATGAGA
TACAGATTGTGCAATTTGTACACTCTTGCGTAGAACATTTCATCTCTTCTAGATTATTA
AACTGAGGGTTTCTTAGATTAAAAAGATGTTTCAAGTGGCCATAGAAAGTAAACAGGT
CTGATTCATATGCTAATTCCTTTTTTAAATGG

LTA4H_30092 (Y=C/T)
ACCCAAGTTCGCACCATTGCACTACAGCCTGGGCAACACAGCAAGACCCTGTCTCCAA
AAAAAAAAAAAAAAGAGCACCTACAATCTTATACCCGGTCTGTTTACAAATAAGTCTG
TCTACTGCTGGTGAACAATGAAATGAAAACCCAGCCTCATTGAGACAGTCTACTAAAC
TCAAAGGAATTCTGATATTAACACCCTTCTCTGAAGCTATTACAAATCCTAAACATACT
TCATTCCACCACAAGCTTTCTTAAAACCCCCAAACTCCAGGTCTTTTCATTTCAGTTCT
AGAAAATTCTCCAAAGATATAGGCTCCCAAATGACCTCTAGATGGATTAAGTAGGACT
AGCAGAGCCACCTGGTTCTCTCTCCCAAAATAGATTTCCAAGACCATGCCTCTATAGTT
CCTTAATGGTTTCTAGTTAGGTGACATGGCAACACCAAAGGGGTTTTTAAATGTATTTC
ATTGGATAAGGCCAAA
[Y]
CCAGGCAAATATGCATACAGAACAACCGTAAGCAAATTCATCAAACAAAATCATGTCT
ACATGATTCCTATCACCTCAATCATTTATTAATTTAGCTGAAATCTGTTTCCCATATTCC
CACCATTGCTGCCAATAAGAAATGGAATAATATATTCAAAATTAACATTTTCATGACT
CATAAATCTTGCATTTCTTGCCAACTTTGGTTAATAGACATTCTATTAAGACATACTGC
CTGAAAATCAGATATTTATGAGATACAGATTGTGCAATTTGTACACTCTTGCGTAGAA
CATTTCATCTCTTCTAGATTATTAAACTGAGGGTTTCTTAGATTAAAAAGATGTTTCAA
GTGGCCATAGAAAGTAAACAGGTCTGATTCATATGCTAATTCCTTTTTTAAATGGACTT
GTATTGAAATTTGAACCTAACACACAGGAATATTGGGAGGGATGAAACATGTAAAGA
ATCTAGCACAATGCCTGGAAATAGAGCA

LTA4H_30271 (Y=C/T)
AAACTCAAAGGAATTCTGATATTAACACCCTTCTCTGAAGCTATTACAAATCCTAAAC
ATACTTCATTCCACCACAAGCTTTCTTAAAACCCCCAAACTCCAGGTCTTTTCATTTCA
GTTCTAGAAAATTCTCCAAAGATATAGGCTCCCAAATGACCTCTAGATGGATTAAGTA
GGACTAGCAGAGCCACCTGGTTCTCTCTCCCAAAATAGATTTCCAAGACCATGCCTCT
ATAGTTCCTTAATGGTTTCTAGTTAGGTGACATGGCAACACCAAAGGGGTTTTTAAATG
TATTTCATTGGATAAGGCCAAACCCAGGCAAATATGCATACAGAACAACCGTAAGCAA
ATTCATCAAACAAAATCATGTCTACATGATTCCTATCACCTCAATCATTTATTAATTTA
GCTGAAATCTGTTTCCCATATTCCCACCATTGCTGCCAATAAGAAATGGAATAATATAT
TCAAAATTAACATTTTCATGACTCA
[Y]
AAATCTTGCATTTCTTGCCAACTTTGGTTAATAGACATTCTATTAAGACATACTGCCTG
AAAATCAGATATTTATGAGATACAGATTGTGCAATTTGTACACTCTTGCGTAGAACATT

FIG. 6.22

TCATCTCTTCTAGATTATTAAACTGAGGGTTTCTTAGATTAAAAAGATGTTTCAAGTGG
CCATAGAAAGTAAACAGGTCTGATTCATATGCTAATTCCTTTTTTAAATGGACTTGTAT
TGAAATTTGAACCTAACACACAGGAATATTGGGAGGGATGAAACATGTAAAGAATCT
AGCACAATGCCTGGAAATAGAGCAAACGTTTAATGAAGTCAGTTCCCTTAATTGTAAA
TTATTTGATTACTATGAAAAGTAGGTATTTTTTCTTTCAGAAGACAGTTTGAAATGTAT
TATCCTTGTGACAGGTTATCTCTAATTGTATGGCTCTTTACCCTTAGTTTTAAAACAGA
AAACAAAAGTAGTTTAAGTCATGCAATTTTA

LTA4H_31036 (Y=C/T)
TTGGGAGGGATGAAACATGTAAAGAATCTAGCACAATGCCTGGAAATAGAGCAAACG
TTTAATGAAGTCAGTTCCCTTAATTGTAAATTATTTGATTACTATGAAAAGTAGGTATT
TTTTCTTTCAGAAGACAGTTTGAAATGTATTATCCTTGTGACAGGTTATCTCTAATTGT
ATGGCTCTTTACCCTTAGTTTTAAAACAGAAAACAAAAGTAGTTTAAGTCATGCAATTT
TAAAGGTACAGTTAATATATTGATATAATACATACTTTTGTAAATGTGTAAGAAAAAT
ATGGAAAAGCTACATTCCAAACTCAATGGTGGTTACCTCTGGGCAATGGTGTCTGGAA
AAGGTTTGGAAATTAAATCTTTCACTTTCCATTTCTTTACTATTAGCATTTTTCATAACC
AGTACATATTATTTATTAATTTTTCCTTTCATTTTATGACTATTTACTGAGTACCTACTC
TCTGCTAAGTTCTAAGTCAGGCCTAGAGAG
[Y]
CCAATCTAGGTGGACATATTTCCAAACTGAAAGAAGCTTCTTATTTAAAGTAAGGCAT
GAGTGTATTAATAGTGAAAGATAAAATGAAAATATATAATTCATCTTATATGTTTCTAT
AAGATCAATTAATACATTTTATTAGGTAAAACCTACATAATCCATAAAACCACTGTTC
ATTTTGCTTCATTCAACCATAGGTGCTGAAATTTTCTGCATCAGAAATCATTCTGGAAT
CCTTTTTACCTGGCACTGACTAAAGAGATATGGGTGTTCCTTCCCAGAAGTCTGTTCAG
GAGTGAGCCACTGGAGAGCAGAAGATTTTGGAGAGGTCTCAAAAGAAATTTCTATAA
CAATTTCTTGATTTCTGTATGAAACACATAAATATATTAGTAGAGTATGATTCCATCTA
GTGAAAATTTAAACTCATAATACATACACTGAATAATATAAATAACATAGTATGCATT
CTCATCACTGATTGGCAGTAAGCTCTAGGTA

LTA4H_31334 (R=A/G)
AAGCTACATTCCAAACTCAATGGTGGTTACCTCTGGGCAATGGTGTCTGGAAAAGGTT
TGGAAATTAAATCTTTCACTTTCCATTTCTTTACTATTAGCATTTTTCATAACCAGTACA
TATTATTTATTAATTTTTCCTTTCATTTTATGACTATTTACTGAGTACCTACTCTCTGCTA
AGTTCTAAGTCAGGCCTAGAGAGTCCAATCTAGGTGGACATATTTCCAAACTGAAAGA
AGCTTCTTATTTAAAGTAAGGCATGAGTGTATTAATAGTGAAAGATAAAATGAAAATA
TATAATTCATCTTATATGTTTCTATAAGATCAATTAATACATTTTATTAGGTAAAACCT
ACATAATCCATAAAACCACTGTTCATTTTGCTTCATTCAACCATAGGTGCTGAAATTTT
CTGCATCAGAAATCATTCTGGAATCCTTTTTACCTGGCACTGACTAAAGAGATATGGGT
GTTCCTTCCCAGAAGTCTGTTCAGGAGT
[R]
AGCCACTGGAGAGCAGAAGATTTTGGAGAGGTCTCAAAAGAAATTTCTATAACAATTT
CTTGATTTCTGTATGAAACACATAAATATATTAGTAGAGTATGATTCCATCTAGTGAAA
ATTTAAACTCATAATACATACACTGAATAATATAAATAACATAGTATGCATTCTCATCA
CTGATTGGCAGTAAGCTCTAGGTATGCCACATCCTCAGTGGGTAAGTCTCCTCTCAGTT
TTCCTACCTAATTGCCAGCCTGTGGGTCCTTTTACCTCTCCCATGCTAACTGCTAGCGA
AGGCTTAATGGCAACTAACAGTGGTTGACTACCCCGTTGTGTGTCACGTACTTTGCATC
TGTGATATCATTTAATATTTTATTAGAGTGAAAAAGTAAAAGAAATCATTTTTGGGGCT
TCAACTACCACAGCAGCAGGTGCCACAGCATGACACAGAGCAGTGCTAGTCTGCAAA
CTGTTACCGGCCCAGGACAAGACAAGACCAG

LTA4H_31627 (R=A/G)
TATATAATTCATCTTATATGTTTCTATAAGATCAATTAATACATTTTATTAGGTAAAAC
CTACATAATCCATAAAACCACTGTTCATTTTGCTTCATTCAACCATAGGTGCTGAAATT
TTCTGCATCAGAAATCATTCTGGAATCCTTTTTACCTGGCACTGACTAAAGAGATATGG
GTGTTCCTTCCCAGAAGTCTGTTCAGGAGTGAGCCACTGGAGAGCAGAAGATTTTGGA
GAGGTCTCAAAAGAAATTTCTATAACAATTTCTTGATTTCTGTATGAAACACATAAATA
TATTAGTAGAGTATGATTCCATCTAGTGAAAATTTAAACTCATAATACATACACTGAAT
AATATAAATAACATAGTATGCATTCTCATCACTGATTGGCAGTAAGCTCTAGGTATGC

FIG. 6.23

CACATCCTCAGTGGGTAAGTCTCCTCTCAGTTTTCCTACCTAATTGCCAGCCTGTGGGT
CCTTTTACCTCTCCCATGCTAACTGCTAGC
[R]
AAGGCTTAATGGCAACTAACAGTGGTTGACTACCCCGTTGTGTGTCACGTACTTTGCAT
CTGTGATATCATTTAATATTTTATTAGAGTGAAAAAGTAAAAGAAATCATTTTTGGGGC
TTCAACTACCACAGCAGCAGGTGCCACAGCATGACACAGAGCAGTGCTAGTCTGCAAA
CTGTTACCGGCCCAGGACAAGACAAGACCAGAAGTTGAGAGTCAGCATTGCAAAACT
TTTAGAGTCATTTTTGTCTGTTGAATCTAATAATAAAAAATGTGTGCTTGTATTTCATCT
CTTCTTCCTCATATTTCATTTTTATTGCATTGTACAAAAGTATCAGTCTATGACAGATTG
AAGAGGATAGAAATTGGTCCTTTACCCCAGAGAGTTTGAGAAGCACTGATAATAAGG
AAACAGCAGAGGTTTAGAGACCAGCAGCCCTGCTGGTGTTCGAATCCTGACTCTATCA
CTTACTGGTACTGTAAACTTGGGGAAATTATT

LTA4H_32435 / SG12S100 (Y=C/T)
GCATTGTACAAAAGTATCAGTCTATGACAGATTGAAGAGGATAGAAATTGGTCCTTTA
CCCCAGAGAGTTTGAGAAGCACTGATAATAAGGAAACAGCAGAGGTTTAGAGACCAG
CAGCCCTGCTGGTGTTCGAATCCTGACTCTATCACTTACTGGTACTGTAAACTTGGGGA
AATTATTTGACCTCCCTATGCCACAGTTTCCTTGTAGAATGGGGTGAATACCATCTACC
TCACAAGCTAGACTTAAGTGTTTCCCTTCTCTTAAAGGGAAAGAGAAGGCATGAAAAC
ACTGGCCTCTGAACAACTGGGGTAGATCACCCTTGTTCTAGGCCAATAGTTTTCACCCT
CTTTCCCCTCAAGAGGTGGCATATACTCCCAGTGTGACAATTCTGGTTGCCACTTTCTT
GAATAAGTTATTTCTCTAAGGTTCCCTTTCCTCATCTTTAAGTGTAGATTATACCAGCA
GGGTTACTGTAAGGATTAGA
[Y]
ACAAGAATGCATTTAAAGCACTTATCCCAAGATTGCTGCACTGTAACAGTTCTATCTTT
GGCATTATCATTGTCCCATTAATAAATGCAGCTGGCCTCTGGGGCAAGGGCAAGGAGG
GTGCAACTTGTAAAGCTGCCCAGGTTATCTTGAAATGCCTTCTTATGATGGCATGCCCC
CACCATCACTCTAGATATTAGTAAAAGGATGAATCGTTTAGAAACTAACAGTTCCCAA
AGTCCTTGTTGTATTATATACAAACAACATTTTTAGTATCTTAAGTATATATAATTTTA
ACTGCTGTATCAACTTTAATCTGAACAGAAGATCAGGATAAGTAGTGTACCAATCATT
ACATATTTACAAACTAAAATTTAAAAAGAAAAAATATTTAAATTAGTTAAGAATATGT
TTCCCCATTATTTAGCTGTAAAAGAGAAAGATCATAACATTCATACTTGCTCAAAGCG
ATAGGAAGAGAGATTTCCATTGGCGAT

LTA4H_32528 (R=A/G)
GGAAACAGCAGAGGTTTAGAGACCAGCAGCCCTGCTGGTGTTCGAATCCTGACTCTAT
CACTTACTGGTACTGTAAACTTGGGGAAATTATTTGACCTCCCTATGCCACAGTTTCCT
TGTAGAATGGGGTGAATACCATCTACCTCACAAGCTAGACTTAAGTGTTTCCCTTCTCT
TAAAGGGAAAGAGAAGGCATGAAAACACTGGCCTCTGAACAACTGGGGTAGATCACC
CTTGTTCTAGGCCAATAGTTTTCACCCTCTTTCCCCTCAAGAGGTGGCATATACTCCCA
GTGTGACAATTCTGGTTGCCACTTTCTTGAATAAGTTATTTCTCTAAGGTTCCCTTTCCT
CATCTTTAAGTGTAGATTATACCAGCAGGGTTACTGTAAGGATTAGATACAAGAATGC
ATTTAAAGCACTTATCCCAAGATTGCTGCACTGTAACAGTTCTATCTTTGGCATTATCA
TTGTCCCATTAATAAATGCAGCT
[R]
GCCTCTGGGGCAAGGGCAAGGAGGGTGCAACTTGTAAAGCTGCCCAGGTTATCTTGAA
ATGCCTTCTTATGATGGCATGCCCCCACCATCACTCTAGATATTAGTAAAAGGATGAAT
CGTTTAGAAACTAACAGTTCCCAAAGTCCTTGTTGTATTATATACAAACAACATTTTTA
GTATCTTAAGTATATATAATTTTAACTGCTGTATCAACTTTAATCTGAACAGAAGATCA
GGATAAGTAGTGTACCAATCATTACATATTTACAAACTAAAATTTAAAAAGAAAAAAT
ATTTAAATTAGTTAAGAATATGTTTCCCCATTATTTAGCTGTAAAAGAGAAAGATCATA
ACATTCATACTTGCTCAAAGCGATAGGAAGAGAGATTTCCATTGGCGATCCCTTGTAA
CTTTGTCTTTCTCCAAGAGCATATTTGACTTCTTGTCCATTGATCACTACTTTTTCTATT
GTAAGGTCCTTTGTATCCAAAACCTAAA

LTA4H_33505 (Y=C/T)
TCCTTTGTATCCAAAACCTAAAATTAATATTTTTAAATAGTAAGAAAATAGTTTCATTT
ACCAGAAAAAAACTCATATTAGATATAGGCTACAACAACTAGTTGCTTATGGAGAGTAA
AATACAGAGTGAAATTAGAAGAATTGAAGAGTCAAAAGCTAGTCTAGGTCTCATTTTT

FIG. 6.24

TGGGACTCTAAGCATCTTGAAAATTTTTGGGTTCTAAGATTTGCATATATATTGTTAAA
TAACCCTAGGACAGTCACACAAATTTTGGGCTTTAAGTAAAAGTCAAATCTAAATCAA
AATATGTTTGCTTCTGACTCCTAAAATTTTCTCTATTATGAAAAACTTTATCTATAACTT
AAGTTTCTTTCACTCTGGCTCCTCAATACATTACACAATATATTTCCTCCTAGAACTCAT
GTACTTTCAAACTTCATGTTCGTTAAGCAAATCAGCAAACTGTATATCACTGTGGTTGT
ATATCTAGAAAAAGCCCAACCTGGTATGG
[Y]
AACTCAGACCAAATGATTCTGCAGAGGATTGGGAGGCCATATCTACTTGCCATGGCCA
ATTAAGGACAACTGCTTTGGGCATGAAGGAGTGACATCAAGTGTCAGAGTATTTTCTA
TCCCCAAAATCCTGAGCCCTACAAATCATACTCTTTAATTATCTCTCAACTAATCTCTT
GTCCTAGAATCTTGAACCTTCCTATGCCACAAGACTGTTTCCTAACAACATAAACAAA
ATTCTACTTGATGGATCTACCCACTAAATATTCTAGTTTTCCTCCTTCCTTCCTTAAACT
CCAAGGGAGTTTTTGACTGCTATGACTACTACTTCTACTTCTTCATTAATCATCCTCCCT
TTCCCCTTCTTCCATCTGGCTTCTTGCTATTGAAAGGGCAGCCCCCACCCCGATCAACA
AAGTCTTTTCTGTCCAATAACCTTGACCTCTGTCTACTCACAGCCCTTATGGACTATGT
CATCTGGTTAAAACCCCTTCCTTCACT

LTA4H_34180 (Y=C/T)
TGTCCTAGAATCTTGAACCTTCCTATGCCACAAGACTGTTTCCTAACAACATAAACAAA
ATTCTACTTGATGGATCTACCCACTAAATATTCTAGTTTTCCTCCTTCCTTCCTTAAACT
CCAAGGGAGTTTTTGACTGCTATGACTACTACTTCTACTTCTTCATTAATCATCCTCCCT
TTCCCCTTCTTCCATCTGGCTTCTTGCTATTGAAAGGGCAGCCCCCACCCCGATCAACA
AAGTCTTTTCTGTCCAATAACCTTGACCTCTGTCTACTCACAGCCCTTATGGACTATGT
CATCTGGTTAAAACCCCTTCCTTCACTTCTTTGCCTGTACGCATACATCATAAATGGTT
CTCTATTTGTCTAATGTTTTTTTCCTTTCCCCTCCTTTATTCCAATTCAAAAATATGGAT
ATGTCCCAATGTTCCAGCCCCGGTCCTTTGATTTTCTTGCCATATCCTTCACTCCCTAGC
TCTTACTCATGCCCACATCTTCAA
[Y]
TAGTATCTCTGTGAAGATGCCTGCCATTCTAGTTCTACAGTTGTATTCCCTCCCCAGGA
CCTCAGTCGAATCGCCTGCTCAACATTTCCATGGGACATAGCACCACACATTGAATAG
GCTTCTAAAAATTCCAAAAATGATTTTTATACTCCCTGAATCAGATTTCTCCCCAGATT
TCTTGATTCTGTTAAAAGAACTCTTCCAGTTACCTAAGGTTTGATCCCATTTCCCAACC
CCACACAGCCACTTAAAAGTTGTTCTTTCACAATGTCTTCATACTTTTCCTTTCTTTCCA
CTACTAACCCAGGTCAGGCCCTGGACTGGCAGAACTGCTTTCTACCAGATCTCCCTACC
TCTGGCATTATTTTTTTCCTTTTCTGAAATCTGACCTGGCTACATGTGAGGCCAAGAAC
CAGCCATTTCCCAGCTGCCCCTGGGTACTTTCTTTTGGGGGTACCTCATTTGTTATCCTT
ACTCTAAATTAGTAGAAGATACGGTT

LTA4H_34314 (R=A/G)
ACTGCTATGACTACTACTTCTACTTCTTCATTAATCATCCTCCCTTTCCCCTTCTTCCAT
CTGGCTTCTTGCTATTGAAAGGGCAGCCCCCACCCCGATCAACAAAGTCTTTTCTGTCC
AATAACCTTGACCTCTGTCTACTCACAGCCCTTATGGACTATGTCATCTGGTTAAAACC
CCTTCCTTCACTTCTTTGCCTGTACGCATACATCATAAATGGTTCTCTATTTGTCTAATG
TTTTTTTCCTTTCCCCTCCTTTATTCCAATTCAAAAATATGGATATGTCCCAATGTTCCA
GCCCCGGTCCTTTGATTTTCTTGCCATATCCTTCACTCCCTAGCTCTTACTCATGCCCAC
ATCTTCAATTAGTATCTCTGTGAAGATGCCTGCCATTCTAGTTCTACAGTTGTATTCCCT
CCCCAGGACCTCAGTCGAATCGCCTGCTCAACATTTCCATGGGACATAGCACCACACA
TTGAATAGGCTTCTAAAAATTCCA
[R]
AAATGATTTTTATACTCCCTGAATCAGATTTCTCCCCAGATTTCTTGATTCTGTTAAAA
GAACTCTTCCAGTTACCTAAGGTTTGATCCCATTTCCCAACCCCACACAGCCACTTAAA
AGTTGTTCTTTCACAATGTCTTCATACTTTTCCTTTCTTTCCACTACTAACCCAGGTCAG
GCCCTGGACTGGCAGAACTGCTTTCTACCAGATCTCCCTACCTCTGGCATTATTTTTTTC
CTTTTCTGAAATCTGACCTGGCTACATGTGAGGCCAAGAACCAGCCATTTCCCAGCTGC
CCCTGGGTACTTTCTTTTGGGGGTACCTCATTTGTTATCCTTACTCTAAATTAGTAGAA
GATACGGTTTATATCTTATTTAAAATAATAGGGTTACTCCTTCATATTCTAGTACCTCTC
TAGTCTCTTCATAGTCTAGTACCTAGTTCTGAATAGCTATTCAGAATAGCTAACTTGTT
TTAAAAACTTGATTTGAGTATCTTG

FIG. 6.25

LTA4H_34505 (Y=C/T)
CTTTGCCTGTACGCATACATCATAAATGGTTCTCTATTTGTCTAATGTTTTTTTCCTTTC
CCCTCCTTTATTCCAATTCAAAAATATGGATATGTCCCAATGTTCCAGCCCCGGTCCTT
TGATTTTCTTGCCATATCCTTCACTCCCTAGCTCTTACTCATGCCCACATCTTCAATTAG
TATCTCTGTGAAGATGCCTGCCATTCTAGTTCTACAGTTGTATTCCCTCCCCAGGACCT
CAGTCGAATCGCCTGCTCAACATTTCCATGGGACATAGCACCACACATTGAATAGGCT
TCTAAAAATTCCAAAAATGATTTTTATACTCCCTGAATCAGATTTCTCCCCAGATTTCT
TGATTCTGTTAAAAGAACTCTTCCAGTTACCTAAGGTTTGATCCCATTTCCCAACCCCA
CACAGCCACTTAAAAGTTGTTCTTTCACAATGTCTTCATACTTTTCCTTTCTTTCCACTA
CTAACCCAGGTCAGGCCCTGGACTGG
[Y]
AGAACTGCTTTCTACCAGATCTCCCTACCTCTGGCATTATTTTTTTCCTTTTCTGAAATC
TGACCTGGCTACATGTGAGGCCAAGAACCAGCCATTTCCCAGCTGCCCCTGGGTACTT
TCTTTTGGGGGTACCTCATTTGTTATCCTTACTCTAAATTAGTAGAAGATACGGTTTAT
ATCTTATTTAAAATAATAGGGTTACTCCTTCATATTCTAGTACCTCTCTAGTCTCTTCAT
AGTCTAGTACCTAGTTCTGAATAGCTATTCAGAATAGCTAACTTGTTTTAAAAACTTGA
TTTGAGTATCTTGTGTTTATAACACATGCTTATATAGATGAATTAACTGGGTCATTTCC
CAGTGGAACATATTCTGTTTTCTATATTGGCTAAACTTTCCAAATCTGTTCAGAATCAG
AAGTGTCATAGTGACAACTATTTTTTGTGAAACGTTTTGATATCCCCTGTGTCTGTTAT
AGCTCTTGGCCCTACCCTTTCCTATAA

LTA4H_34600 (Y=C/T)
CCCAATGTTCCAGCCCCGGTCCTTTGATTTTCTTGCCATATCCTTCACTCCCTAGCTCTT
ACTCATGCCCACATCTTCAATTAGTATCTCTGTGAAGATGCCTGCCATTCTAGTTCTAC
AGTTGTATTCCCTCCCCAGGACCTCAGTCGAATCGCCTGCTCAACATTTCCATGGGACA
TAGCACCACACATTGAATAGGCTTCTAAAAATTCCAAAAATGATTTTTATACTCCCTGA
ATCAGATTTCTCCCCAGATTTCTTGATTCTGTTAAAAGAACTCTTCCAGTTACCTAAGG
TTTGATCCCATTTCCCAACCCCACACAGCCACTTAAAAGTTGTTCTTTCACAATGTCTT
CATACTTTTCCTTTCTTTCCACTACTAACCCAGGTCAGGCCCTGGACTGGCAGAACTGC
TTTCTACCAGATCTCCCTACCTCTGGCATTATTTTTTTCCTTTTCTGAAATCTGACCTGG
CTACATGTGAGGCCAAGAACCAGCCA
[Y]
TTCCCAGCTGCCCCTGGGTACTTTCTTTTGGGGGTACCTCATTTGTTATCCTTACTCTAA
ATTAGTAGAAGATACGGTTTATATCTTATTTAAAATAATAGGGTTACTCCTTCATATTC
TAGTACCTCTCTAGTCTCTTCATAGTCTAGTACCTAGTTCTGAATAGCTATTCAGAATA
GCTAACTTGTTTTAAAAACTTGATTTGAGTATCTTGTGTTTATAACACATGCTTATATA
GATGAATTAACTGGGTCATTTCCCAGTGGAACATATTCTGTTTTCTATATTGGCTAAAC
TTTCCAAATCTGTTCAGAATCAGAAGTGTCATAGTGACAACTATTTTTTGTGAAACGTT
TTGATATCCCCTGTGTCTGTTATAGCTCTTGGCCCTACCCTTTCCTATAATACTTACTGT
ACTGCATTATAATGATTTCTTTTTCCATTAGACTAAGGGTTCTAAAACAGAGAATGTTA
CTTAGGTCTGTATTCCCAGGGTTTAG

LTA4H_34723 (Y=C/T)
GTATTCCCTCCCCAGGACCTCAGTCGAATCGCCTGCTCAACATTTCCATGGGACATAGC
ACCACACATTGAATAGGCTTCTAAAAATTCCAAAAATGATTTTTATACTCCCTGAATCA
GATTTCTCCCCAGATTTCTTGATTCTGTTAAAAGAACTCTTCCAGTTACCTAAGGTTTG
ATCCCATTTCCCAACCCCACACAGCCACTTAAAAGTTGTTCTTTCACAATGTCTTCATA
CTTTTCCTTTCTTTCCACTACTAACCCAGGTCAGGCCCTGGACTGGCAGAACTGCTTTC
TACCAGATCTCCCTACCTCTGGCATTATTTTTTTCCTTTTCTGAAATCTGACCTGGCTAC
ATGTGAGGCCAAGAACCAGCCATTTCCCAGCTGCCCCTGGGTACTTTCTTTTGGGGGTA
CCTCATTTGTTATCCTTACTCTAAATTAGTAGAAGATACGGTTTATATCTTATTTAAAAT
AATAGGGTTACTCCTTCATATTCTAG
[Y]
ACCTCTCTAGTCTCTTCATAGTCTAGTACCTAGTTCTGAATAGCTATTCAGAATAGCTA
ACTTGTTTTAAAAACTTGATTTGAGTATCTTGTGTTTATAACACATGCTTATATAGATG
AATTAACTGGGTCATTTCCCAGTGGAACATATTCTGTTTTCTATATTGGCTAAACTTTC
CAAATCTGTTCAGAATCAGAAGTGTCATAGTGACAACTATTTTTTGTGAAACGTTTTGA
TATCCCCTGTGTCTGTTATAGCTCTTGGCCCTACCCTTTCCTATAATACTTACTGTACTG
CATTATAATGATTTCTTTTTCCATTAGACTAAGGGTTCTAAAACAGAGAATGTTACTTA

FIG. 6.26

GGTCTGTATTCCCAGGGTTTAGCACTCTGCCTCAAAAACACTAGGTGTCAATTAATGCA
TGAAGCAGGTCCTAGACCAAGAGAAAACAAAAAATGCAATGTTTAAGCTGTATTATCT
CAAGTCCTAAGTCTCAACTATCATTTGC

LTA4H_35490 (R=A/G)
ACCCTTTCCTATAATACTTACTGTACTGCATTATAATGATTTCTTTTTCCATTAGACTAA
GGGTTCTAAAACAGAGAATGTTACTTAGGTCTGTATTCCCAGGGTTTAGCACTCTGCCT
CAAAAACACTAGGTGTCAATTAATGCATGAAGCAGGTCCTAGACCAAGAGAAAACAA
AAAATGCAATGTTTAAGCTGTATTATCTCAAGTCCTAAGTCTCAACTATCATTTGCAAA
CTACTTTTTAAAATTCCCCTTCAAATTTCAGCGATGTTATTTTTAAAAAATAGTCAAAA
ACTGTAATAAGAAAGAAAAATAAAGAAAACTGGATTGTTGACAAGTTGGATTTAGTA
CTTTTTAAGAAACGTGTTAAGCATCAACAGCTCTACTAATTATAGGATATAATTTATAT
GTTTCACAGTATCCTCTTTGAACAATACCCTCCATCCCCCTAAAAAGCAGTTGTACTTC
TCAGTAGCTGGTCAGTTGACATGGAATAG
[R]
TATCTGATTCCTTTTTTGCACAGGCTGGTAGGAAGCTCCATGTCAACCCTGTGGCCCAC
TTCTTTTAAAGTATAGAGGGCTTTATGCCATGGGTTTTGTTTCTCCTATCCCTATTCTCT
CTTCCTGCAAATTATTTAATTATTTTTAATCTTATACTATATATGTTGCTTCAAGCAGTC
TCAGTCCTTTCTAGAACAAAGCAGAGTTTTTTTAAAAAAAGCTTTATGCCTCATTATGA
TGTCTAAATTTACATTTTCTACTTGCTATGTGCAGGGATATGATGAAAAAAAATAGGTT
TATGTGTGAAACACAAAGCTAAAACTAAAAAACCACCTTGATTTGATTCCCAGTTGAG
ACATTTACTTAGTGAAAACAAGATGGTTTGCAGTCAGAATTACCTATTGTTAACTGCTG
GCTTCTGCCTTGGCCATGGCACTAAAACCTCTTGAGCCACTAACCAAAAGAACACCTA
AACATTTCTGAAGGTTTCAGTGAAAAGA

LTA4H_35549 (Y=C/T)
GTTCTAAAACAGAGAATGTTACTTAGGTCTGTATTCCCAGGGTTTAGCACTCTGCCTCA
AAAACACTAGGTGTCAATTAATGCATGAAGCAGGTCCTAGACCAAGAGAAAACAAAA
AATGCAATGTTTAAGCTGTATTATCTCAAGTCCTAAGTCTCAACTATCATTTGCAAACT
ACTTTTTAAAATTCCCCTTCAAATTTCAGCGATGTTATTTTTAAAAAATAGTCAAAAAC
TGTAATAAGAAAGAAAAATAAAGAAAACTGGATTGTTGACAAGTTGGATTTAGTACTT
TTTAAGAAACGTGTTAAGCATCAACAGCTCTACTAATTATAGGATATAATTTATATGTT
TCACAGTATCCTCTTTGAACAATACCCTCCATCCCCCTAAAAAGCAGTTGTACTTCTCA
GTAGCTGGTCAGTTGACATGGAATAGGTATCTGATTCCTTTTTTGCACAGGCTGGTAGG
AAGCTCCATGTCAACCCTGTGGCCCA
[Y]
TTCTTTTAAAGTATAGAGGGCTTTATGCCATGGGTTTTGTTTCTCCTATCCCTATTCTCT
CTTCCTGCAAATTATTTAATTATTTTTAATCTTATACTATATATGTTGCTTCAAGCAGTC
TCAGTCCTTTCTAGAACAAAGCAGAGTTTTTTTAAAAAAAGCTTTATGCCTCATTATGA
TGTCTAAATTTACATTTTCTACTTGCTATGTGCAGGGATATGATGAAAAAAAATAGGTT
TATGTGTGAAACACAAAGCTAAAACTAAAAAACCACCTTGATTTGATTCCCAGTTGAG
ACATTTACTTAGTGAAAACAAGATGGTTTGCAGTCAGAATTACCTATTGTTAACTGCTG
GCTTCTGCCTTGGCCATGGCACTAAAACCTCTTGAGCCACTAACCAAAAGAACACCTA
AACATTTCTGAAGGTTTCAGTGAAAAGAAACAAATGTATGAAAGTTATCATAAATTTG
GAGGATCAAACTTCAGTGTAAATAACCCA

LTA4H_36055 / SG13S28 (K=G/T)
TTAAAGTATAGAGGGCTTTATGCCATGGGTTTTGTTTCTCCTATCCCTATTCTCTCTTCC
TGCAAATTATTTAATTATTTTTAATCTTATACTATATATGTTGCTTCAAGCAGTCTCAGT
CCTTTCTAGAACAAAGCAGAGTTTTTTTAAAAAAAGCTTTATGCCTCATTATGATGTCT
AAATTTACATTTTCTACTTGCTATGTGCAGGGATATGATGAAAAAAAATAGGTTTATGT
GTGAAACACAAAGCTAAAACTAAAAAACCACCTTGATTTGATTCCCAGTTGAGACATT
TACTTAGTGAAAACAAGATGGTTTGCAGTCAGAATTACCTATTGTTAACTGCTGGCTTC
TGCCTTGGCCATGGCACTAAAACCTCTTGAGCCACTAACCAAAAGAACACCTAAACAT
TTCTGAAGGTTTCAGTGAAAAGAAACAAATGTATGAAAGTTATCATAAATTTGGAGGA
TCAAACTTCAGTGTAAATAACCCAAAACT
[K]
GAAAAGAATTTTAGAAAGCTTAGAATTTGTCCGATTAAGTCTCCTTCAGCATTCCTCAA
CATCACAAACTCTAAGAACGGAGAGGAAAAGAAGACATGACGTCTCTCCTGATTCCGC

FIG. 6.27

ACTGGCACTGGGTCTTCCCATCTCACCTCTGAAATACAGCTGGCACTATTATCAATGTA
GCCCATGTTAAGCTTAGGCACTGTTTTCTAATTGAAATCATCCATTAATCAAACTTTTG
AATGTCCTCTACATGCCAGACATAGACTATACTAGGAAGCTGAGATACAAAGAGTTAT
GAAACACAGTCTCTACATTCAAGAGTCCACAATCTAGTGGAGGAAAGAAACAAGTTA
ACTTTAAATAAATACTAATTAACTAATTAATAAGGATAAGCTCCTGGTCTAAGGCTTTT
GTCATAAATAAGCAAACAATTATAAACATGTTATTTTGTACCATAAATTGCCTTCCTTG
TATAACATGTAACATTATTATAAT

LTA4H_36330 (Y=C/T)
AGACATTTACTTAGTGAAAACAAGATGGTTTGCAGTCAGAATTACCTATTGTTAACTG
CTGGCTTCTGCCTTGGCCATGGCACTAAAACCTCTTGAGCCACTAACCAAAAGAACAC
CTAAACATTTCTGAAGGTTTCAGTGAAAAGAAACAAATGTATGAAAGTTATCATAAAT
TTGGAGGATCAAACTTCAGTGTAAATAACCCAAAACTTGAAAAGAATTTTAGAAAGCT
TAGAATTTGTCCGATTAAGTCTCCTTCAGCATTCCTCAACATCACAAACTCTAAGAACG
GAGAGGAAAAGAAGACATGACGTCTCTCCTGATTCCGCACTGGCACTGGGTCTTCCCA
TCTCACCTCTGAAATACAGCTGGCACTATTATCAATGTAGCCCATGTTAAGCTTAGGCA
CTGTTTTCTAATTGAAATCATCCATTAATCAAACTTTTGAATGTCCTCTACATGCCAGA
CATAGACTATACTAGGAAG
[Y]
TGAGATACAAAGAGTTATGAAACACAGTCTCTACATTCAAGAGTCCACAATCTAGTGG
AGGAAAGAAACAAGTTAACTTTAAATAAATACTAATTAACTAATTAATAAGGATAAGC
TCCTGGTCTAAGGCTTTTGTCATAAATAAGCAAACAATTATAAACATGTTATTTTGTAC
CATAAATTGCCTTCCTTGTATAACATGTAACATTATTATAATTCCAGGCTCTAATTTGC
TAAACAGACATGCCAACCAGAAATCACTATTTTAAAATCTTACTTTTCTCTAGATTTGG
GGAATGTAAAAACAATGAGCAGATTTTTAGATTGGGACATTCTTTTCAAAATTTAAAC
ATCCTGACTCTTGCTTACTTATAGAACAGAGATAAAGTTTTTATTCTACAAAAGTGATG
AGAACACATGGATACACAGTGGGGAACACACACTGGGGCTTACTGGAGGGTGGAGGG
TAGGAGAAGGGAAAGGATCAGGA

LTA4H_36560 (Y=C/T)
AGAAAGCTTAGAATTTGTCCGATTAAGTCTCCTTCAGCATTCCTCAACATCACAAACTC
TAAGAACGGAGAGGAAAAGAAGACATGACGTCTCTCCTGATTCCGCACTGGCACTGG
GTCTTCCCATCTCACCTCTGAAATACAGCTGGCACTATTATCAATGTAGCCCATGTTAA
GCTTAGGCACTGTTTTCTAATTGAAATCATCCATTAATCAAACTTTTGAATGTCCTCTA
CATGCCAGACATAGACTATACTAGGAAGCTGAGATACAAAGAGTTATGAAACACAGT
CTCTACATTCAAGAGTCCACAATCTAGTGGAGGAAAGAAACAAGTTAACTTTAAATAA
ATACTAATTAACTAATTAATAAGGATAAGCTCCTGGTCTAAGGCTTTTGTCATAAATAA
GCAAACAATTATAAACATGTTATTTTGTACCATAAATTGCCTTCCTTGTATAACATGTA
ACATTATTATAATTCCAGGCTCTAA
[Y]
TTGCTAAACAGACATGCCAACCAGAAATCACTATTTTAAAATCTTACTTTTCTCTAGAT
TTGGGGAATGTAAAAACAATGAGCAGATTTTTAGATTGGGACATTCTTTTCAAAATTT
AAACATCCTGACTCTTGCTTACTTATAGAACAGAGATAAAGTTTTTATTCTACAAAAGT
GATGAGAACACATGGATACACAGTGGGGAACACACACTGGGGCTTACTGGAGGGTGG
AGGGTAGGAGAAGGGAAAGGATCAGGAAAAGTAACTAATGGGTACTAGGCTTAATAC
CTGGGTGACAAAATAATCTGTACAACAAACCCTCATGACACAAGTTTACCTATGTAAC
AAACCTGCACATTTGAAGTACACCTGAACTTCAAATAATAAATTTTTTAAGTTTTTATT
TTACAAAACAAAGGTAAGTGTGAGGTCACATTAAGCAGCAAAAAGCTATAAAAATTTT
CATTCTTTTACTTTTATCAGCATA

LTA4H_36773 (Y=C/T)
AATCAAACTTTTGAATGTCCTCTACATGCCAGACATAGACTATACTAGGAAGCTGAGA
TACAAAGAGTTATGAAACACAGTCTCTACATTCAAGAGTCCACAATCTAGTGGAGGAA
AGAAACAAGTTAACTTTAAATAAATACTAATTAACTAATTAATAAGGATAAGCTCCTG
GTCTAAGGCTTTTGTCATAAATAAGCAAACAATTATAAACATGTTATTTTGTACCATAA
ATTGCCTTCCTTGTATAACATGTAACATTATTATAATTCCAGGCTCTAATTTGCTAAAC
AGACATGCCAACCAGAAATCACTATTTTAAAATCTTACTTTTCTCTAGATTTGGGGAAT
GTAAAAACAATGAGCAGATTTTTAGATTGGGACATTCTTTTCAAAATTTAAACATCCTG

FIG. 6.28

ACTCTTGCTTACTTATAGAACAGAGATAAAGTTTTTATTCTACAAAAGTGATGAGAAC
ACATGGATACACAGTGGGGAACACACA
[Y]
TGGGGCTTACTGGAGGGTGGAGGGTAGGAGAAGGGAAAGGATCAGGAAAAGTAACTA
ATGGGTACTAGGCTTAATACCTGGGTGACAAAATAATCTGTACAACAAACCCTCATGA
CACAAGTTTACCTATGTAACAAACCTGCACATTTGAAGTACACCTGAACTTCAAATAA
TAAATTTTTTAAGTTTTTATTTTACAAAACAAAGGTAAGTGTGAGGTCACATTAAGCAG
CAAAAAGCTATAAAAATTTTCATTCTTTTACTTTTATCAGCATAGTTTATAATTTAATTT
TTTTAAATAAAGGTGAAGAACAAGAACTTTCCAGTTAACTAAGAGCTTTGAGTGGGTT
TGGGGCTTAGTCAAGGTTTTATTATATCTTAAACCAATTGGAATATTTCTTCTGAAATA
TATGTTGCAGCTAAAGATTCAAGGAAGAATTTGCTGTTCATATATTAGAAAAACCTCTT
TAAATTTCTTCCACTAGCGACCTCGGT

LTA4H_36803 (R=A/G)
CATAGACTATACTAGGAAGCTGAGATACAAAGAGTTATGAAACACAGTCTCTACATTC
AAGAGTCCACAATCTAGTGGAGGAAAGAAACAAGTTAACTTTAAATAAATACTAATTA
ACTAATTAATAAGGATAAGCTCCTGGTCTAAGGCTTTTGTCATAAATAAGCAAACAAT
TATAAACATGTTATTTTGTACCATAAATTGCCTTCCTTGTATAACATGTAACATTATTAT
AATTCCAGGCTCTAATTTGCTAAACAGACATGCCAACCAGAAATCACTATTTTAAAAT
CTTACTTTTCTCTAGATTTGGGGAATGTAAAAACAATGAGCAGATTTTTAGATTGGGAC
ATTCTTTTCAAAATTTAAACATCCTGACTCTTGCTTACTTATAGAACAGAGATAAAGTT
TTTATTCTACAAAAGTGATGAGAACACATGGATACACAGTGGGGAACACACACTGGG
GCTTACTGGAGGGTGGAGGGTAGGA
[R]
AAGGGAAAGGATCAGGAAAAGTAACTAATGGGTACTAGGCTTAATACCTGGGTGACA
AAATAATCTGTACAACAAACCCTCATGACACAAGTTTACCTATGTAACAAACCTGCAC
ATTTGAAGTACACCTGAACTTCAAATAATAAATTTTTTAAGTTTTTATTTTACAAAACA
AAGGTAAGTGTGAGGTCACATTAAGCAGCAAAAAGCTATAAAAATTTTCATTCTTTTA
CTTTTATCAGCATAGTTTATAATTTAATTTTTTTAAATAAAGGTGAAGAACAAGAACTT
TCCAGTTAACTAAGAGCTTTGAGTGGGTTTGGGGCTTAGTCAAGGTTTTATTATATCTT
AAACCAATTGGAATATTTCTTCTGAAATATATGTTGCAGCTAAAGATTCAAGGAAGAA
TTTGCTGTTCATATATTAGAAAAACCTCTTTAAATTTCTTCCACTAGCGACCTCGGTTTT
GGTTTGCAATTATTCACATCTGAACACAAGTG

LTA4H_37351 (Y=C/T)
CTGGGTGACAAAATAATCTGTACAACAAACCCTCATGACACAAGTTTACCTATGTAAC
AAACCTGCACATTTGAAGTACACCTGAACTTCAAATAATAAATTTTTTAAGTTTTTATT
TTACAAAACAAAGGTAAGTGTGAGGTCACATTAAGCAGCAAAAAGCTATAAAAATTTT
CATTCTTTTACTTTTATCAGCATAGTTTATAATTTAATTTTTTTAAATAAAGGTGAAGAA
CAAGAACTTTCCAGTTAACTAAGAGCTTTGAGTGGGTTTGGGGCTTAGTCAAGGTTTTA
TTATATCTTAAACCAATTGGAATATTTCTTCTGAAATATATGTTGCAGCTAAAGATTCA
AGGAAGAATTTGCTGTTCATATATTAGAAAAACCTCTTTAAATTTCTTCCACTAGCGAC
CTCGGTTTTGGTTTGCAATTATTCACATCTGAACACAAGTGTCCTGAATTGCTTAATTTT
TAAATCTCTAGTACTTTTGAATGTAGGA
[Y]
GTATAAACTCATGTTCAAATATGGCAGTCTCACAGTGTGGTTTTTCTTTTTTTATTATTA
TACTTTAAGTTCTGGGGTACATGTGCAGAACGTGCAGGTTTGTTACATAAGTATACAC
ATGCCATGGTGGTTTGCTGCACCCATCAACCCGTCAGCTACATTAGGTATTTCTCCTAA
TGCTATCCCTCCCCTAGGCCCCTACCCCCAACAGGCCCTGGTGTGTGATGTTCCCCTCC
CTGTGTCCATGTGTTCTCATTGTTCAACTCTCACTTATGAGTGAGAACATGCGGTGTTT
AGTTTTGAAACTGCATTGAAATAGGACTTCAGCCCTGCCCAGGCAAAGTTGCTACTGC
AATTAAAGATAGCATGGTACTTCAAGAAGACCAAAGTGCGATCTGCAAGGAAATAGA
TGCCTTCCTGCTTATAATATCTTAATTTTCTTTCTTATGGTACTTTTGTTGATTACCTATC
AGTACATAGAGGAATCGACCTATTTTTC

LTA4H_37360 (H=A/T/C)
AAAATAATCTGTACAACAAACCCTCATGACACAAGTTTACCTATGTAACAAACCTGCA
CATTTGAAGTACACCTGAACTTCAAATAATAAATTTTTTAAGTTTTTATTTTACAAAAC
AAAGGTAAGTGTGAGGTCACATTAAGCAGCAAAAAGCTATAAAAATTTTCATTCTTTT

FIG. 6.29

ACTTTTATCAGCATAGTTTATAATTTAATTTTTTTAAATAAAGGTGAAGAACAAGAACT
TTCCAGTTAACTAAGAGCTTTGAGTGGGTTTGGGGCTTAGTCAAGGTTTTATTATATCT
TAAACCAATTGGAATATTTCTTCTGAAATATATGTTGCAGCTAAAGATTCAAGGAAGA
ATTTGCTGTTCATATATTAGAAAAACCTCTTTAAATTTCTTCCACTAGCGACCTCGGTTT
TGGTTTGCAATTATTCACATCTGAACACAAGTGTCCTGAATTGCTTAATTTTTAAATCT
CTAGTACTTTTGAATGTAGGACGTATAAAC
[H]
CATGTTCAAATATGGCAGTCTCACAGTGTGGTTTTTCTTTTTTTATTATTATACTTTAAG
TTCTGGGGTACATGTGCAGAACGTGCAGGTTTGTTACATAAGTATACACATGCCATGG
TGGTTTGCTGCACCCATCAACCCGTCAGCTACATTAGGTATTTCTCCTAATGCTATCCC
TCCCCTAGGCCCCTACCCCCAACAGGCCCTGGTGTGTGATGTTCCCCTCCCTGTGTCCA
TGTGTTCTCATTGTTCAACTCTCACTTATGAGTGAGAACATGCGGTGTTTAGTTTTGAA
ACTGCATTGAAATAGGACTTCAGCCCTGCCCAGGCAAAGTTGCTACTGCAATTAAAGA
TAGCATGGTACTTCAAGAAGACCAAAGTGCGATCTGCAAGGAAATAGATGCCTTCCTG
CTTATAATATCTTAATTTTCTTTCTTATGGTACTTTTGTTGATTACCTATCAGTACATAG
AGGAATCGACCTATTTTTCAAATCAATC

LTA4H_37526 (W=A/T)
CATTCTTTTACTTTTATCAGCATAGTTTATAATTTAATTTTTTTAAATAAAGGTGAAGAA
CAAGAACTTTCCAGTTAACTAAGAGCTTTGAGTGGGTTTGGGGCTTAGTCAAGGTTTTA
TTATATCTTAAACCAATTGGAATATTTCTTCTGAAATATATGTTGCAGCTAAAGATTCA
AGGAAGAATTTGCTGTTCATATATTAGAAAAACCTCTTTAAATTTCTTCCACTAGCGAC
CTCGGTTTTGGTTTGCAATTATTCACATCTGAACACAAGTGTCCTGAATTGCTTAATTTT
TAAATCTCTAGTACTTTTGAATGTAGGACGTATAAACTCATGTTCAAATATGGCAGTCT
CACAGTGTGGTTTTTCTTTTTTTATTATTATACTTTAAGTTCTGGGGTACATGTGCAGAA
CGTGCAGGTTTGTTACATAAGTATACACATGCCATGGTGGTTTGCTGCACCCATCAACC
CGTCAGCTACATTAGGTATTTCTCC
[W]
AATGCTATCCCTCCCCTAGGCCCCTACCCCCAACAGGCCCTGGTGTGTGATGTTCCCCT
CCCTGTGTCCATGTGTTCTCATTGTTCAACTCTCACTTATGAGTGAGAACATGCGGTGT
TTAGTTTTGAAACTGCATTGAAATAGGACTTCAGCCCTGCCCAGGCAAAGTTGCTACT
GCAATTAAAGATAGCATGGTACTTCAAGAAGACCAAAGTGCGATCTGCAAGGAAATA
GATGCCTTCCTGCTTATAATATCTTAATTTTCTTTCTTATGGTACTTTTGTTGATTACCT
ATCAGTACATAGAGGAATCGACCTATTTTTCAAATCAATCAGTTTAGCAAAATGTTGA
GGGATGAAGAGTAAGAAAGTAAGTACTTATTAGTTCATATTAATGAAATCAAAATTCA
GATCCTTCCTACACAAGTAGGAAAAAGAGGCCTGAAAGCCACCAATTCTTATCTGCCC
GATCTGATCTGATTGCTTATTGATGTGCTTTAG

LTA4H_37634 (M=A/C)
TCAAGGTTTTATTATATCTTAAACCAATTGGAATATTTCTTCTGAAATATATGTTGCAG
CTAAAGATTCAAGGAAGAATTTGCTGTTCATATATTAGAAAAACCTCTTTAAATTTCTT
CCACTAGCGACCTCGGTTTTGGTTTGCAATTATTCACATCTGAACACAAGTGTCCTGAA
TTGCTTAATTTTTAAATCTCTAGTACTTTTGAATGTAGGACGTATAAACTCATGTTCAA
ATATGGCAGTCTCACAGTGTGGTTTTTCTTTTTTTATTATTATACTTTAAGTTCTGGGGT
ACATGTGCAGAACGTGCAGGTTTGTTACATAAGTATACACATGCCATGGTGGTTTGCT
GCACCCATCAACCCGTCAGCTACATTAGGTATTTCTCCTAATGCTATCCCTCCCCTAGG
CCCCTACCCCCAACAGGCCCTGGTGTGTGATGTTCCCCTCCCTGTGTCCATGTGTTCTC
ATTGTTCAACTCTCACTTATGAGTGAGA
[M]
CATGCGGTGTTTAGTTTTGAAACTGCATTGAAATAGGACTTCAGCCCTGCCCAGGCAA
AGTTGCTACTGCAATTAAAGATAGCATGGTACTTCAAGAAGACCAAAGTGCGATCTGC
AAGGAAATAGATGCCTTCCTGCTTATAATATCTTAATTTTCTTTCTTATGGTACTTTTGT
TGATTACCTATCAGTACATAGAGGAATCGACCTATTTTTCAAATCAATCAGTTTAGCAA
AATGTTGAGGGATGAAGAGTAAGAAAGTAAGTACTTATTAGTTCATATTAATGAAATC
AAAATTCAGATCCTTCCTACACAAGTAGGAAAAAGAGGCCTGAAAGCCACCAATTCTT
ATCTGCCCGATCTGATCTGATTGCTTATTGATGTGCTTTAGTAGATTTCACCATGCTAC
ACTGTGTAAAATACACATGTAGCATCCTGCCCTGGTGAAGAAGCCGAATTTGGCTGTC
TTTTCATGACCCTCTTATTTTTAAAATG

FIG. 6.30

LTA4H_37933 (K=G/T)
GAACGTGCAGGTTTGTTACATAAGTATACACATGCCATGGTGGTTTGCTGCACCCATC
AACCCGTCAGCTACATTAGGTATTTCTCCTAATGCTATCCCTCCCCTAGGCCCCTACCC
CCAACAGGCCCTGGTGTGTGATGTTCCCCTCCCTGTGTCCATGTGTTCTCATTGTTCAA
CTCTCACTTATGAGTGAGAACATGCGGTGTTTAGTTTTGAAACTGCATTGAAATAGGA
CTTCAGCCCTGCCCAGGCAAAGTTGCTACTGCAATTAAAGATAGCATGGTACTTCAAG
AAGACCAAAGTGCGATCTGCAAGGAAATAGATGCCTTCCTGCTTATAATATCTTAATT
TTCTTTCTTATGGTACTTTTGTTGATTACCTATCAGTACATAGAGGAATCGACCTATTTT
TCAAATCAATCAGTTTAGCAAAATGTTGAGGGATGAAGAGTAAGAAAGTAAGTACTTA
TTAGTTCATATTAATGAAATCAAAAT
[K]
CAGATCCTTCCTACACAAGTAGGAAAAAGAGGCCTGAAAGCCACCAATTCTTATCTGC
CCGATCTGATCTGATTGCTTATTGATGTGCTTTAGTAGATTTCACCATGCTACACTGTG
TAAAATACACATGTAGCATCCTGCCCTGGTGAAGAAGCCGAATTTGGCTGTCTTTTCAT
GACCCTCTTATTTTTAAAATGATCTTCTATGAAATTCTTCAGGTGAAAGGTACCTTCAG
ATGAAAGGTATAAACCAAATACTATTGGGCAATTTGAGCAAGAACATTAAATATAGGT
TATGATACAGATAAAATCATTGAATAATATTCCATGAATCTACAACCTTTCTTCATTCC
AATGGTTATAGAGTTTGTAGAAGTATGTGTTTTCTAAGTGAAATAACTACTTGGCTCCT
TGGAACCAACTATTAAAAAAGCGTATTGAATCATCCTTAGAAAATTTGAACGTCCCAT
CCGTTCTTAAATTATTAGAAGAAAGTTG

LTA4H_37947 (Y=C/T)
TTGTTACATAAGTATACACATGCCATGGTGGTTTGCTGCACCCATCAACCCGTCAGCTA
CATTAGGTATTTCTCCTAATGCTATCCCTCCCCTAGGCCCCTACCCCCAACAGGCCCTG
GTGTGTGATGTTCCCCTCCCTGTGTCCATGTGTTCTCATTGTTCAACTCTCACTTATGAG
TGAGAACATGCGGTGTTTAGTTTTGAAACTGCATTGAAATAGGACTTCAGCCCTGCCC
AGGCAAAGTTGCTACTGCAATTAAAGATAGCATGGTACTTCAAGAAGACCAAAGTGC
GATCTGCAAGGAAATAGATGCCTTCCTGCTTATAATATCTTAATTTTCTTTCTTATGGT
ACTTTTGTTGATTACCTATCAGTACATAGAGGAATCGACCTATTTTTCAAATCAATCAG
TTTAGCAAAATGTTGAGGGATGAAGAGTAAGAAAGTAAGTACTTATTAGTTCATATTA
ATGAAATCAAAATTCAGATCCTTCCTA
[Y]
ACAAGTAGGAAAAAGAGGCCTGAAAGCCACCAATTCTTATCTGCCCGATCTGATCTGA
TTGCTTATTGATGTGCTTTAGTAGATTTCACCATGCTACACTGTGTAAAATACACATGT
AGCATCCTGCCCTGGTGAAGAAGCCGAATTTGGCTGTCTTTTCATGACCCTCTTATTTT
TAAAATGATCTTCTATGAAATTCTTCAGGTGAAAGGTACCTTCAGATGAAAGGTATAA
ACCAAATACTATTGGGCAATTTGAGCAAGAACATTAAATATAGGTTATGATACAGATA
AAATCATTGAATAATATTCCATGAATCTACAACCTTTCTTCATTCCAATGGTTATAGAG
TTTGTAGAAGTATGTGTTTTCTAAGTGAAATAACTACTTGGCTCCTTGGAACCAACTAT
TAAAAAAGCGTATTGAATCATCCTTAGAAAATTTGAACGTCCCATCCGTTCTTAAATTA
TTAGAAGAAAGTTGATAAGATTAAAA

LTA4H_38836 (K=G/T)
TTGGCTCCTTGGAACCAACTATTAAAAAAGCGTATTGAATCATCCTTAGAAAATTTGA
ACGTCCCATCCGTTCTTAAATTATTAGAAGAAAGTTGATAAGATTAAAAAGTAGAAAG
GACCCTGAAGAGAGAGAGCTGCGCCTAGAGTTAGCAAGCAGGGACTGTTAGTTTCAA
AGTAGGGCGGAAAGAAGAGGCCTGCCCGGCCGGGGCTGGAAATCCTAAGAGGCTTGA
GAACGACTAGCAGGGAGATCCAGGGAACTAGGAGGGAGACGGATGGGTGGTGCCCTG
CAGACCTGTGGATTGAAATAAGTGTTCCCGGGAGGCAACCGTGGGATCAGGGATCGA
CAGGACATGGGATCTGAGACTTGGGTGAGATTGTTGACTGAGGAAGGTGCCCAGGGG
GCTGGGAAAAGTCTGGGGCCTGAAGAAGGGGGTTCTGGGCCGCAGGCCGAAGCAATG
GGGAGGCCATGGAGTAATTAGAGCCAGGAACTAAAATTATGG
[K]
GGCTACTGCAAAGATGACACCTAAGGGCTGGGTGAGTTGAGAGGAGTGGACGAGGCG
CTGGATGTGCCCAGGGACCTCGGAGAGAGGATCCAGGCGAGGGGCGGAGGAGACATA
CGTATAAGTGGGGGCTGAGGGAAGGGATGCAGAGGCGTAAGCGGGGTTGAGAAGGG
GTGCTGTGAGAGATCTGGGGGCTGAAGTGCACAACATGAGTTGGATGGAGGCTACAG
AAGAGCAGACGGGGACGTGGGGCTAGGCAGGGGCCGCGGCGGGGTGAGCCGGAGAT
CCGGGAGCCCGCAAGGACTAGGGTCGAGGGGCAGGGAGCCCGGGAGAGGCGGGCAC

FIG. 6.31

TGGGCAGGCGCCCCACTGTACCAGGCTGCGCAGATTGTCCTCCTGAGACTGGACCGTG
AGAGCAGCAGTCCCGGTCAGCGTCCGGCGAGTAAAGTCGACGCTGCAGCGCAGGTGC
AGGTGCTTGGTCCGGCAGACGGAAGCCGGAGAGGCCAACGAACAGG

SG12S141 **(R=A/G)**
AGTAAAGATTTCAGAGGTGTGAGGGATAGTTGATGGGTTTAGCATGCTGGTATGGTTC
AATTCTCTATCAAAAGTGACGAAATTTAGCTCCAGCAACAACAACAAAAAAACTGCTAT
ATTTCTGGATATCCTTGTGTTGGCCCCTGCAAGCCAAAGGAAAACAAAATAAAACCAA
AAAATCCCAAACTATGAAATCTAATACCTTACACATGCATAGGTCCTAATTCATAGGG
TGTAAGAATTTGTCATCAACATTTGCATTTTCGGATTTTTTTGGCAAATGTCCTGTTGCC
CAGGCTGGATACAGTGGCATGATCATGGGTAACTGCACATTCAACCTCCTGGACTCAA
GCGATTCTCGTGCCTCAGCCTCCAAGTAGCTGGGACTACAGGCGCCC
[R]
CCACCACGCCTGGCTAATTTTTATATTTTTTAGAGATGGGGTTTTGTCATGTTGCCCA
AGCTGGTCTCAAACTTCTGAGCTCAAGGGATCCACCTGCCTTGGCCTTCCAAAGTGCTG
GGATTACAGGTACGAGCCACCACACAGAGCCGCAAACATTTTTTGAGGTCACCAAATC
TAGGGTGACAAATACAATAGATAACATAGAATTCATTTAGTCAAATAATACACAGTCA
AATCATCTTATTTATCTAGTATGGAGAAAGGATAGTTTGTTTTAATAAGAACGTCATTA
TCATCATCTTCTATTATTGATTACCAGGAACCCACAGAGTTTATGCCACTTGTGTTTAA
ATAAAAATATCCACACACAACCACAAATAAATTCCTCCATTAATATATTCATCAAAAA
ATAAATTACAGTAGGAATTGTTTTCTGAGATACCACTCACCCCAAATATAGAATGTAC
AAAATTTGCAATTTACAAGCAATTGGAGTATTATTGATATCCA

SG12S144 **(R=A/G)**
CTCGATGAAGAAGGAAAACCAAGGAAGTCCGTGTCTTGGATGACAAGTGACATCTGG
AAAAATAAAGGAGCAGTGTGGTCAGGGAGCCTGATGAAATTCTGACTATGGATGACT
CACTGTTTTGTGTAAAAAGGGGGAAGAGAATTTATTCTAAAAATTTGTTCATATCTACA
TAAAATACTTCTGGAGGGATGCTCAAGAAACTCATGGTATTGTTTGCCTGTGTGGACA
GAGAAGGAAGGCCAAAGAACAGAGGTGAAAAGTAGATATTTCAACTGAATAATCTTG
TAAGCCTTTTGAATTTTAATGTGAATATATTTCCCAGTCAAAAGGTTATTTATTGATAT
GAAAAAAAATAAAGGTCACTGGAATCCCAAACCACAAACAAAAACAGCCCTTGCTGA
CTTCCTGTGGACTTCATAGTGTCTACCACTGGCCCC
[R]
CGGGGCTCTGCAGCTTCCACTTGAGTGGCTCGATACACCCTGCGTCAGCCATGCTGAA
CCAAGGTGTTCAAGCTCTCTGCACTCTCTGGCCCTTCCTTGAGCCTGCATGCCCTTCCC
ACTCCCACTCTTCCCGCAACCTTGGCAGGGCTCTCCTCCTCCCCTTCAGGACTCTGCCC
CCCACCACCCTCCAGTCTGGGCTAGAGTCTAGTAGAATCTCCCTTGCTAAGAGAACAA
GGTGCATGTGACACCCTTCTCTTCCTCCCTTCAGTGTGTGAGCAAATAGAAGAAATGAT
TTTAGCCACATTTTTAATGTTCACCTTACAACATAGTTGAGGCAATCCTGACCAGTTTC
TCCATCTTCTGTGAAATTTCTTCTTCCTTGTGCAGCCATGCGCATGAATTCTAT

FIG. 6.32

SG12S140:

ATTTGCATTTTCGGATTTTTTTGGCAAATGTCCTGTTGCCCAGGCTGGATACAGTGGCATG
ATCATGGGTAACTGCACATTCAACCTCCTGGACTCAAGCGATTCTCGTGCCTCAGCCTCCA
AGTAGCTGGGACTACAGGCGCCCGCCACCACGCCTGGCTAATTTTTATATTTTTTTAGAGA
TGGGGTTTTGTCATGTTGCCCAAGCTGGTCTCAAACTTCTGAGCTCAAGGGATCCACCTGC
CTTGGCCTTCCAAAGTGCTGGGATTACAGGTACGAGCCACCACACAGAGCCGCAAACATT
TTTTGAGGTCACCAAATCTAGGGTGACAAATACAATAGATA

[A/C]

CATAGAATTCATTTAGTCAAATAATACACAGTCAAATCATCTTATTTATCTAGTATGGAGA
AAGGATAGTTTGTTTTAATAAGAACGTCATTATCATCATCTTCTATTATTGATTACCAGGA
ACCCACAGAGTTTATGCCACTTGTGTTTAAATAAAAATATCCACACACAACCACAAATAA
ATTCCTCCATTAATATATTCATCAAAAAATAAATTACAGTAGGAATTGTTTTCTGAGATAC
CACTCACCCCAAATATAGAATGTACAAAATTTGCAATTTACAAGCAATTGGAGTATTATTG
ATATCCAATGGGGAATTGAGAATGCTTCAAAAAATGAGGCTTTCCACTGCATCTATAAAA
GAAG

SG12S143:

TTTGTTTAAGACAGTGTTATCTTGGGTTTTCTGTCCTTCACAGGGAACTCAATCTTTACTAA
GACTCCTGGTCTCAGTTGGGTGAGTTTATCAGTTTTGCCCCAGATACTTGCCCTTATCTGTT
GGTTTTCCACCACATTATCGTGGACAGATCTTTCTTCCTTCTTGCTTGTGTTATCTGCTAGA
GCATTCTTTCTAATGTAATCATCTCACTCCCCTGCTTAAAATCCTTCAAGGTCTTACTAACA
TTGCCAGTTGATATTATCTGCCTTTTTTGATTTAAGGCCCATTTTCAAATACTAGAATTTTT
GGCATACAATCCAAGGGATTAAAAGATGAA

[C/T]

GTAAGCTTTTTTTTTAAAGAAAGCTTTGGCAAATTTTTTTTAAATAACCAGTTATTCACAGT
ATATTATAATATTATATTTGTATGCTTTTATGATTTTTTAAATCTGAAATTATATTAAAATG
AAAGATGAGTCTCATTTCTTGTATAAGTTCACTTTTTTGTTGTTGTTGTTTTGGCATTTGAT
GTTTGTAAGAGTTGAGAACCCTAATTTTCTGAGAAATGACATGGAAGACTGCAGCAGTAC
CTCTGGACTCCACAGTTGGGTGCTCTTCGAGACCATGTTGCCATTTAAACAGAATGGTTTC
CTCCCTTTGCTCTGCCTGCTGATGTGGTCTAGCTAGCTCCTGATTAAACTCTGCCTCTTG

SG12S221:

TCTAGGCTGTGCACACTCACTGCTGTACAGTGTTCCATGTGTGGATATACCATGATTTACT
TATCCTTTCAACCGTGGATAGACATGTGGGTGATTTCCAGTTCTGAGTTATTATTATGAAT
GGTGCTGCTATGGATATTCTGGTACGTGTCTTTCGGTGAACACATTGTAGCCAGGTTTTGA
CATGCTGCTTTGAAGTTTAGACAGTTGCACCCTGCCAGGAGATTTCCTTTAAGACCCCTGC
ACCAGGCCAGAAACATTCACTGCATTGCAGCAACCTGATTCTGTAGTTGTTGACACAAATC
CAACACCCTTCTCCCTACCCCAGCTTGGGTAGGGGTTAAAAGTAGATGAA

[A/G]

TAGGGAGGGAAGCTGTTTTCAAGTTACAAGAAAAAGTTCTTTACAACTGCTGGCCTTGTTC
ATACTTTATTTTCCTCTCACTCACTTCCGTTTCTTTTCCAGGTAAGCCTGATTGCAAGCTTC
ATTGTACCTGTTTCTTTCTGACTCAGATTCCAGCTCAGCTTACATTTTTCCCACTAAGTAGG
CAGTGATATTTCATCACAGCAGGTACTTACACCTTTTGTTCTGATGACTTAAAGCACAAGT
AGGTTTTGATAAGTGCTTGCAGGGTTTCATTTTCAAAAGTCCTATTTCTGTGTCATATTTGT
TGGCTTTGAGCCCAGTTTCTCTTGCTCTGCCAACAGAGCAGGTTATGCCTATTT

FIG. 7.1

SG12S222:

TTTTTTCAAACTTTTCTTCTCCCTCTCCTCATCCTCTACTCCTTGATCTTCACTTGGAGAAGG
ACAATTCTAGAATTCCTGAACTCTAGGCCAAAAGGAAGTGGGCAATCATGGCAAGCATAA
ACACATCCATGGCAAGTTATCAGACACCTTTTGTGGGTACTAAACAGCAGGGATGCCCAC
TTGTCCCTTGGAAGTTTGCAAACATACTGGGAAAATGGGGACTATAAAATTAAACCACCA
AAGATCAGTGTGGGAGACTGAATAATTAAAGGGTATCCAGGTGGACCAGTCACAAACGCT
GTAGGAGCTCAATGGAGACATCAGTGGGCA

[C/T]

CTTCCTGGAAGCAGTGAGGCTTGCATGGAAATAAAAAACAGGGGGTTCTAATTTTTGTTAT
TGTTCACCAATATCAGCAAAAAAGGTGGGCACACCCCTCAATAAATGTTTGCAAATTCTTTA
CATGTGCTAATTAATCATATCTTAAGATGCAAAATACATTGAGGGCAAGGTTTACTCTTAA
CAATGGTCAATGTAAATCCTTACTTTAAATAAGCATCTTATAATTATGATTTGCATGGGGG
GCACATTTTGTCAGATCTTATTTGTCATCATTATTTTGTTTTGTTTGTTAATACACTCATCTT
ATCTTGGAGTAGGAGAATTATTAGGTCTGTTAATCTTTCTTGTTGCTCACTGTTATTTTG

SG12S223:

TATGAACCAGAAAATGGGCCCTCACCAGACATCACATCTGCTGGCATCTTTATCAAGGAC
TTCTCAGCCTCCAAAATTGTGAGAAATAAATTTCTGTTGTGCATAAGCTACCCAGTCTATG
GTATTTTGTTATAGCAGCCTGAATGGACTAAGACACACTTATTGAACCCCCACGTGTTTTT
CTGAAGAATGAATGCCTCACATTTTACACAAGATGTCTGTGTGCACTGGGGCCGTCTAGTC
TACCCTGGCCTGGTGATCAGGGCAGGGAATCA

[C/T]

TGAAGTTTCCCATTCTCTAAAAGTGGAGGAAATGGCAGCCATGGGGAAGCTGCCTTCTGC
TAACACAATTGAGCCGTGAAAACAATATACAACTATTTTTGTTATATTCCAGTGGTCACAC
AGAGCAACCCCAATACAATAGGAGGGCACACCCACAAAGCCATGAGTACCAGGAGGGGTG
ATCACTGGGAGACTCCTTGGAAGCTGGCTGCCACTGTGAGGCATTATCTCTGTTTCACAGA
GGAGAAACAGAAGCTCCAATAAATAATTGCTCAAGTCAACTCAACTTGGAACAGGCAGGT
CTGGGGTTCAAACCCAGACAATGAGACCCCAGAACACATCCTTTTAGAACACTGCCCTAT
ACCCTGGCCTCACCACAGGCCTTTTTTTCTAACTTCCTCTCTTCCCCTCACCGCGCAAAACA
TTGCAAATGAGATTTTT

SG12S224

GAGGGCACACCACAAAGCCATGAGTACCAGGAGGGGTGATCACTGGGAGACTCCTTGGA
AGCTGGCTGCCACTGTGAGGCATTATCTCTGTTTCACAGAGGAGAAACAGAAGCTCCAAT
AAATAATTGCTCAAGTCAACTCAACTTGGAACAGGCAGGTCTGGGGTTCAAACCCAGACA
ATGAGACCCCAGAACACATCCTTTTAGAACACTGCCCTATACCCTGGCCTCACCACAGGCC
TTTTTTTCTAACTTCCTCTCTTCCCCTCACCGCGCAAAACATTGCAAATGAGATTTTTCCTT
TTTCTTAGACCATTTCAAAAGTCATTGTTACTTAAGGGTGGAGGTTGGAAGATTTCCAAAG
AATAAAATATACAGAGAATATCTAACCAAAGTTCCTAACACATACACAATTCAGAAAATG
TAACTCACAGACAAGGGATAACAAGACCATTGACCCA

[A/G]

TTTCAGAGCTTGACGTTTACAAAATGAACACAAGGCAGTGTGGGTTGTATGCGCGTTCTGT
TCAGTTTCTCTCCTTTGGGGTTGTTTGGGTCAGCCTGTTGTCTCATGAGACTGGGTGGGCTA
AATTGAGCAACATTTTGCTATAATAAGTCTGCAAGATTAGACCTTAGGCAACAAAAGCCG
GAAGGAGAAACTACATTTCCTATAAAATGTGGAACTGTGGGATAACAGTGTAACAACACT
ATGACTACAAACAGGGAAATTTATATATGAGAAGGAACTGGATTGTATGTTACCTATATA

FIG. 7.2

AATGATCATGAGAAAGTCATGTTGTTCTTTTGTTGTGATCTTTTAAACCAAATTTATAGTGC
ATTGAACCAAGTAATTGTAGGCCATTATTTTAAAGTAGGTTGTAGCACAGCATGAATTAA

SG12S225

GAGGAGGTGATGTACACTTTTAAAAAACCTAATCTCACAAGCACTCACTCACTATCACGG
GAACAGCACCAAAGGAACAGCACCAAGGCGATGATGCGAAACCATTCATGAGAAATCCG
CCCCCATGATCCAATCACCTCCCCGCCAGGCCCCACCTCCAACACTGGGGACTACAATTCC
ACATGGATTTGATGGGAACACACACCCAAGCCATGTCTGATGGACACATAGTTTATTTTCT
TTTGTGACTCTGCATAGGCCATTCTTGCCACTGGGACCCCTTCCCTCCCAATCCTCCTGGCT
TTCCCTGCCTGTCAGCAAACTCCTGCTCCTTTTTCAAGCATCAACTCGGATTTACCCTCTGC
TGTGATGTCTTCTGTGACTCACATGCAGATTTAGGCACCTGTTTATT

[A/G]

TGTTCTCAATATATCTTACCCATACTATAGAAATATTTGTTGTTTTTTATCTACCTAGTGTT
AAATTAAATAAGCACGAGGCCATTGGCCAGAGGCCCTCTCCATATTTTGAGTTTCTGTGGA
ACAAACAGCAACCTAATAGTATGTAAACAAACTGAAACCTAATTTAGGAGTATATTTTTG
TAACATATAGCCTGGTTTCAGCCAATCACAGAGAAGCTTCAGCCAATAATAAGCATCCAA
TTGATGAGACCACGCCCAATAAGGCAGATGCCTAGCTGTTGCCGATCAAGTGGTTTCTCTA
CATTGCTTTTGTGTTCACCCTAGAAAAGCTCATTGCTCACACTGCCAAGTGGAGTTTTCTG
AACCTCTTCTGGTTCTGAGTGCTGCCTGATTCATGAATCATTCTTTGCCCAAATAAAC

SG12S226

GTTTCTCTACATTGCTTTTGTGTTCACCCTAGAAAAGCTCATTGCTCACACTGCCAAGTGG
AGTTTTCTGAACCTCTTCTGGTTCTGAGTGCTGCCTGATTCATGAATCATTCTTTGCCCAAA
TAAACTCTGTTAAATTTAATTTGTCTAAACTGTTTCTTTTAACACTAGCTTCTATTCCGCCT
TCTCTGACAAGCGTTCAGGAACCCACCCCACCCCCACCCCGTACTTTGGGTGTAGCCCATG
TGATTTAAGTCTAGCCAATCAGAGCACTAAGGAGCTACAGTTCAGAGGTGATCATGAGAC
CCAGGTTCATCGAACTAGAGTGAATCCTGGGACT

[C/G]

AGCATGAGCGGCTGGGAAGAAACACACAAGTTTTTGTTGCAAGTCTGGAGCTGCTAGCAG
ACTTCACATACTGCCTGAGCATGAAGCAAAAATAAAGAGAGTGAAAAGAATGAGAGAGA
ATGGGAAAGAGTCTGCTGGTGACATTATTTGATCCTCTGAATGATGCCTCACTTAAATTCA
AGATATATTCTTGGATTTTGTGCATTAACAAATTCCCTTTTTGAGCTTAAGCCTGCTTGATT
TATCTATCATTTGCAACCAAAGGAACATTAACCAATAAATACATTTCACTGTATATCTGTG
TCTATATATCTATATGTATTTCATTTTACCAAGGTGTCTCCCTACTAACCATAATTCTTT

SG12S227

AACTAGAGTGAATCCTGGGACTGAGCATGAGCGGCTGGGAAGAAACACACAAGTTTTTGT
TGCAAGTCTGGAGCTGCTAGCAGACTTCACATACTGCCTGAGCATGAAGCAAAAATAAAG
AGAGTGAAAAGAATGAGAGAGAATGGGAAAGAGTCTGCTGGTGACATTATTTGATCCTCT
GAATGATGCCTCACTTAAATTCAAGATATATTCTTGGATTTTGTGCATTAACAAATTCCCTT
TTTGAGCTTAAGCCTGCTTGATTTATCTATCATTTGCAACCAAAGGAACATTAACCAATAA
ATACATTTCACTGTATATCTGTGTCTATATATCT

[A/G]

TATGTATTTCATTTTACCAAGGTGTCTCCCTACTAACCATAATTCTTTGAGGGCAGTAGAT
GCTCAATATTTGTCAAATGAATTCAGCTGAAGGGTGTTTTGAAGGAGACTGACCTTAGAG
GAGGGACATTTTAGGAAGGCTAATGGACTTAGTGTGAGATGTGATCAAGGGACTCAACCA
AGTTGAAGAGTAGGATTGAAAGGGAAGGGACAAATACCAAAGAAAGATTTAACAAGGCA
GTGATACAGAGTGGGGTGGAGCAATAGTTAGATTAAAGCCTGAGTGCTACCCTGTTCTGC
GTATTTGTTTCTTTTGGTGTCTCTTTAGCAGCCAGCCTAAATTAAAAGTTTATTGTACTGGC
TGATTATTGCCTGTCTAAATCACCCGTCTCTGTTAGTTTATCACAAGTGAAAAAATTA

FIG. 7.3

SG12S228

TAGAGTGAATCCTGGGACTGAGCATGAGCGGCTGGGAAGAAACACACAAGTTTTTGTTGC
AAGTCTGGAGCTGCTAGCAGACTTCACATACTGCCTGAGCATGAAGCAAAAATAAAGAGA
GTGAAAAGAATGAGAGAGAATGGGAAAGAGTCTGCTGGTGACATTATTTGATCCTCTGAA
TGATGCCTCACTTAAATTCAAGATATATTCTTGGATTTTGTGCATTAACAAATTCCCTTTTT
GAGCTTAAGCCTGCTTGATTTATCTATCATTTGCAACCAAAGGAACATTAACCAATAAATA
CATTTCACTGTATATCTGTGTCTATATATCTATA

[C/T]

GTATTTCATTTTACCAAGGTGTCTCCCTACTAACCATAATTCTTTGAGGGCAGTAGATGCT
CAATATTTGTCAAATGAATTCAGCTGAAGGGTGTTTTGAAGGAGACTGACCTTAGAGGAG
GGACATTTTAGGAAGGCTAATGGACTTAGTGTGAGATGTGATCAAGGGACTCAACCAAGT
TGAAGAGTAGGATTGAAAGGGAAGGGACAAATACCAAAGAAAGATTTAACAAGGCAGTG
ATACAGAGTGGGGTGGAGCAATAGTTAGATTAAAGCCTGAGTGCTACCCTGTTCTGCGTA
TTTGTTTCTTTTGGTGTCTCTTTAGCAGCCAGCCTAAATTAAAAGTTTATTGTACTGGCTGA
TTATTGCCTGTCTAAATCACCCGTCTCTGTTAGTTTATCACAAGTGAAAAAATTAATG

SG12S229

GGCTGGGAAGAAACACACAAGTTTTTGTTGCAAGTCTGGAGCTGCTAGCAGACTTCACAT
ACTGCCTGAGCATGAAGCAAAAATAAAGAGAGTGAAAAGAATGAGAGAGAATGGGAAA
GAGTCTGCTGGTGACATTATTTGATCCTCTGAATGATGCCTCACTTAAATTCAAGATATAT
TCTTGGATTTTGTGCATTAACAAATTCCCTTTTTGAGCTTAAGCCTGCTTGATTTATCTATC
ATTTGCAACCAAAGGAACATTAACCAATAAATACATTTCACTGTATATCTGTGTCTATATA
TCTATATGTATTTCATTTTACCAAGGTGTCTCCCTA

[A/C]

TAACCATAATTCTTTGAGGGCAGTAGATGCTCAATATTTGTCAAATGAATTCAGCTGAAGG
GTGTTTTGAAGGAGACTGACCTTAGAGGAGGGACATTTTAGGAAGGCTAATGGACTTAGT
GTGAGATGTGATCAAGGGACTCAACCAAGTTGAAGAGTAGGATTGAAAGGGAAGGGACA
AATACCAAAGAAAGATTTAACAAGGCAGTGATACAGAGTGGGGTGGAGCAATAGTTAGA
TTAAAGCCTGAGTGCTACCCTGTTCTGCGTATTTGTTTCTTTTGGTGTCTCTTTAGCAGCCA
GCCTAAATTAAAAGTTTATTGTACTGGCTGATTATTGCCTGTCTAAATCACCCGTCTCTGTT
AGTTTATCACAAGTGAAAAAATTAATGATAGAGAATCAGAGACTCACATATAAGCAA

SG12S230

ACCAATAAATACATTTCACTGTATATCTGTGTCTATATATCTATATGTATTTCATTTTACCA
AGGTGTCTCCCTACTAACCATAATTCTTTGAGGGCAGTAGATGCTCAATATTTGTCAAATG
AATTCAGCTGAAGGGTGTTTTGAAGGAGACTGACCTTAGAGGAGGGACATTTTAGGAAGG
CTAATGGACTTAGTGTGAGATGTGATCAAGGGACTCAACCAAGTTGAAGAGTAGGATTGA
AAGGGAAGGGACAAATACCAAAGAAAGATTTAACAAGGCAGTGATACAGAGTGGGGTGG
AGCAATAGTTAGATTAAAGCCTGAGTGCTACCCTGTTCTGCGTATTTGTTTCTTTTGGTGTC
TCTTTAGCAGCCAGCCTAAATTAAAAGTTTATTGT

[A/G]

CTGGCTGATTATTGCCTGTCTAAATCACCCGTCTCTGTTAGTTTATCACAAGTGAAAAAAT
TAATGATAGAGAATCAGAGACTCACATATAAGCAAATAAGCATGATTATTATAAGAAAGA
GCTTTTATTAAACAATACTTTCAGGTCTTCATAAGAATAGGGGTAGAATTTCAGAGACCCA
CATAACTCAGTGTGCAGTAAATGCTGCTCCTGGGCAACTTAATGGAGCATAAACTGCCAG
CAACGGTCCCAATTGAAATGGAGACTGGAAGGTGAAGTTGTCCTTCCTTTCTGTAACCACC
AGGCAAGAGGACACTTGTAAGGTGTGAGTAGCAGCACCCAAAAACCAGCTGCAGGAC

SG12S231

FIG. 7.4

GGGGTGGAGCAATAGTTAGATTAAAGCCTGAGTGCTACCCTGTTCTGCGTATTTGTTTCTT
TTGGTGTCTCTTTAGCAGCCAGCCTAAATTAAAAGTTTATTGTACTGGCTGATTATTGCCTG
TCTAAATCACCCGTCTCTGTTAGTTTATCACAAGTGAAAAAATTAATGATAGAGAATCAGA
GACTCACATATAAGCAAATAAGCATGATTATTATAAGAAAGAGCTTTTATTAAACAATAC
TTTCAGGTCTTCATAAGAATAGGGGTAGAATTTCAGAGACCCACATAACTCAGTGTGCAG
TAAATGCTGCTCCTGGGCAACTTAATGGAGCATAAACTGCCAGCAACGGTCCCAATTGAA
ATGGAGACTGGAAGGTGAAGTTGTCCTTCCTTTC

[C/T]

GTAACCACCAGGCAAGAGGACACTTGTAAGGTGTGAGTAGCAGCACCCAAAAACCAGCT
GCAGGACTCAGTGGAAGGGAGGAATAAGGTCACTCTTAAAATCCTATCACCTCACATAGA
AAAATAGCTAAGTCCTAATTAAGCTCAACATCGCCACTCTCAGCTTATCCCTGAGACAGGT
CAGGAGAAGAGGGACCATTTGCTTTGCTCTGGGATTGTTGCACTTCTGCAATCTGACTTTG
TAAAAAAAAAAAAAATTAATTTAAACAGTTGCTACCATATGGGATAGTGTAGCTCGATGG
TTTCTTTCTCTCTCTCGTCCCTCTCCTGCTCTGCCTTCTATGTATTTACCACCCCTCTT

SG12S232

TGGTGAAGTGTGAATCATTTCTCCATGTAAAACACATAGGACAGGCTGGGCATGGTGGCT
CACGCCTGTAATCCCAGCACTTTAGGAGGCCTAGGCGGGTGGATCACCTGAGGTCAGGAG
TTCAAGACCAGCCTGGGCAACATGGAGAAACCCCATCTCTACTGAAAATACAAAAATTAG
CTGTGCGTGATGGCGCACACCTGTAATCCCAGTTACTCGGGAGACTGAGGCAGGAGAATC
ACTTGAACCCGGGAGCGGAGGTTGCGGTGAGCCGAGATCGTGCCATTGCACTTAAGCCTG
GGTTACAAGAGCGAAACTCTGTCTCAAAACAAAACACACATAGGA

[C/T]

AGAGCTCAGCACAGAGTAGACATTAAGGATTATATCCTTTGCTTGGCACAATACCTTGCAC
AGGGCAGGCACGCAACAGATGTCTCTGGAATGAAGGAATGAATGAGTGAATGACTGGGT
TAAGCATGTTGCCACCAGGTGGCAGAAGAGCCTCACTATCAAGGCAGAACCCAAACACGA
GACTCATGAGAACTCCCTCCTGAAGTCCAGATACACATTGAAAAAAAATAAAAAAAGCAC
TGAACCCCATTTAGGCCTTGAAGTGAAGTTCCTCTTCTCTCTTGCCCTTCCTTTCTCT

SG12S233

AAGACCAGCCTGGGCAACATGGAGAAACCCCATCTCTACTGAAAATACAAAAATTAGCTG
TGCGTGATGGCGCACACCTGTAATCCCAGTTACTCGGGAGACTGAGGCAGGAGAATCACT
TGAACCCGGGAGCGGAGGTTGCGGTGAGCCGAGATCGTGCCATTGCACTTAAGCCTGGGT
TACAAGAGCGAAACTCTGTCTCAAAACAAAACACACATAGGACAGAGCTCAGCACAGAG
TAGACATTAAGGATTATATCCTTTGCTTGGCACAATACCTTGCACAGGGCAGGCACGCAA
CAGATGTCTCTGGAATGAAGGAATGAATGAGTGAATGACTGGGTTAAGCATGTTGCCACC
AGGTGGCAGAAGAGCCTCACTATCAAGGCAGAACCCAAACACGAGA

[C/T]

TCATGAGAACTCCCTCCTGAAGTCCAGATACACATTGAAAAAAAATAAAAAAAGCACTGA
ACCCCATTTAGGCCTTGAAGTGAAGTTCCTCTTCTCTCTTGCCCTTCCTTTCTCTCCCATCTC
TGCTCACTCTCTGCTGTAATGAACCATTTCTTTCTTTCCCACTTAATACATATTAGTCAGTT
TGGGCTGCCACAGCAAAATACTACAGACTCAGTAGTTTAAACAACAGATATTTAATGCAT
CACAGTTCTGGAGGTTGGAAGTCCATGATCAAAGTGCCATACGGGCTGGTTTCTGGTGAG
GCTTCTCTTCCTGGCTTGTAGCTGTCCACCTTCCCACTGTTATTCTCACAGGGCCT

SG12S234

GATCCCCAGAGGTGTCTGTTATGCACAGTAAGCTCCAACAGTGAAAAATCATTTATAAAG
GGCCGAGGACAGTGGCTTGCACCTGCAATCCCAGCACTTTGGGAGGTCATGGTGGGCAGA
TTGCTTAAGCCCAGGAGTTCCAGACCAGCCTGGGCAACATGGCAAAACACCATCTCTACT
AAAAATTTAAAAACTTAGTTAGGTGTGGTGGCTGGCACCTGTAGTCGCAGCTACTTGGGA

FIG. 7.5

GGGTGAGGTAGGCGGATCACTTGAACCTGGGAGGTTGAAGCTGCAGTGAGCTGTAATCAT
GCCACTGCACTCCAGCCTGGATGACAGAGCAAGACCCTGTCTCAAAAAAAA

[A/G]

AAAAAATTATCAAGGACTTTTGCCTCTAATAAAATATTCACAGTGGTTTCCTTACTTAATT
TCTGAGGTCAAACCAGAAAATATTAGCAGCTGACTTAATTCAAGAAGGAGGAGCTTGAGT
ATACGTACTTGTTGGTGTGTCTTCAACTCTTGTTCTAGATTTTACTTTGTTTTAAATATGTA
AAAATGCTTTTAGTGATTACAACTTATGCTTCTTATTTCAACAGATATTTTAAAGGGAAAA
ATATATAATTGGATCACAGGATATAAAAAGAAATGCAGTTATCTATATGTGCAAAAGCCT
AGCTAATTGATAAAAGCTATAAGTTGAGTCCTGCCACTCACCTTGGGGCAATGATTTTTTA
TTT

SG12S235

ATCATTTATAAAGGGCCGAGGACAGTGGCTTGCACCTGCAATCCCAGCACTTTGGGAGGT
CATGGTGGGCAGATTGCTTAAGCCCAGGAGTTCCAGACCAGCCTGGGCAACATGGCAAAA
CACCATCTCTACTAAAAATTTAAAAACTTAGTTAGGTGTGGTGGCTGGCACCTGTAGTCGC
AGCTACTTGGGAGGGTGAGGTAGGCGGATCACTTGAACCTGGGAGGTTGAAGCTGCAGTG
AGCTGTAATCATGCCACTGCACTCCAGCCTGGATGACAGAGCAAGACCCTGTCTCAAAAA
AAAGAAAAAATTATCAAGGACTTTTGCCTCTAATAAAATATTCACAGTGG

[C/T]

TTCCTTACTTAATTTCTGAGGTCAAACCAGAAAATATTAGCAGCTGACTTAATTCAAGAAG
GAGGAGCTTGAGTATACGTACTTGTTGGTGTGTCTTCAACTCTTGTTCTAGATTTTACTTTG
TTTTAAATATGTAAAAATGCTTTTAGTGATTACAACTTATGCTTCTTATTTCAACAGATATT
TTAAAGGGAAAAATATATAATTGGATCACAGGATATAAAAAGAAATGCAGTTATCTATAT
GTGCAAAAGCCTAGCTAATTGATAAAAGCTATAAGTTGAGTCCTGCCACTCACCTTGGGG
CAATGATTTTTTATTTATTTATTTTATTTTATTATTATTATTTTTTTAGACAGAGTTGCCCAG

SG12S236

TTTGTATTTATAGTAGACATGGAGTTTCACCATCTTGGCCAGGATGGTTCCGAACTCCTGA
CCTCGTGATCCACCACTCGGCCTCCCAAAATGCTGGGATTACAAGCATAAGCCACTGCAC
CACGCCCGGCCAATGACCCATTTTTTTCAGGCAAAGTAGCAATGGGAAAATATAAAGTTT
CTCTAGTTTTAATATAGAAGTGGTTAACCTAATCACACAAGCCATACACAGGGTCATTTGG
GAGAATGTGCAAGGAGGATTGCGTATTTTTATCTTTTCATAGTTTTCTTCTTGATAAATAA
GCTTCTATTTTCAAGCCAAATCTCATCTTGCAATTTCCTGCCAACTTCACTTCTCTACAAAG
TTTACCTTTGCTTTTCCCATCTCTGCCCT

[C/G]

AGGCATTTAACAAACACTGTGCCTTTTCATTTTTCCAGATTTAAGTGAAACATTTTGCAGA
AATGAGGAATGTGATAACAGCCCCTGAAGCCCTACCTGACAGCATGACATTAATTTGGGC
CTGTTTTCTCTCATACTTTTCAATTGCTCCCCAATTTATATTTAATTTGCCACAGGATATAA
AAAGAAATATTTCTTTAATTTATATTAAATACATCTACATTAGGAGAGCTAGAGGTTATCT
AAGTGAAACTAGCTCGATTATCTAAAAAAAGTCAGAATAAAATAATTATAAGCAAATTGG
AAGAACAGCCAACGTTGTTACCAATAATTTCTTAGAGTTTGTTCAATTATTGTTTGTTATAC
T

SG12S237

TTATCTTTTCATAGTTTTCTTCTTGATAAATAAGCTTCTATTTTCAAGCCAAATCTCATCTTG
CAATTTCCTGCCAACTTCACTTCTCTACAAAGTTTACCTTTGCTTTTCCCATCTCTGCCCTC
AGGCATTTAACAAACACTGTGCCTTTTCATTTTTCCAGATTTAAGTGAAACATTTTGCAGA
AATGAGGAATGTGATAACAGCCCCTGAAGCCCTACCTGACAGCATGACATTAATTTGGGC
CTGTTTTCTCTCATACTTTTCAATTGCTCCCCAATTTATATTTAATTTGCCACAGGATATAA
AAAGAAATATTTCTTTAATTTATATTAAATACATCTACATTAGGAGAGCTAGAGGTTATCT

FIG. 7.6

AAGTGAAACTAGCTCGATTATCTAAAAAAAGTCAGAATAAAATAATTATAAGCAAATTGG
AAGAACAGCCAACGTTGTTACCAATAATTT

[C/T]

TTAGAGTTTGTTCAATTATTGTTTGTTATACTCTGTTTCCACTTCTTTAGCCAAAATAAGCT
CTAAGCAAATTCAAATCTATTTGTATAGATGAAGTCTATGAATTTAACATGATAACTTGAA
AAAATGTAAAACTTTGGCTGGGTGTGGTGGCTCACACCTGTAATCCCAGCACTGTGGGAG
GCTGTGGCGGGCGGATCACCTAAGGTCGGGAGCTCCAGACCAGCCTGGCCAACATTGTGA
AACCCCATCTCTACTAAAAATACAAGCATTAGCGAGGCATGGTGGTGGGCACCTGTAATC
CCAGCTACTCAGGAGGCTGAGGCAGGAGAATCGCTTGAACCCAGGAGGCGGAGGT

SG12S238

TGCAGAAATGAGGAATGTGATAACAGCCCCTGAAGCCCTACCTGACAGCATGACATTAAT
TTGGGCCTGTTTTCTCTCATACTTTTCAATTGCTCCCCAATTTATATTTAATTTGCCACAGG
ATATAAAAAGAAATATTTCTTTAATTTATATTAAATACATCTACATTAGGAGAGCTAGAGG
TTATCTAAGTGAAACTAGCTCGATTATCTAAAAAAAGTCAGAATAAAATAATTATAAGCA
AATTGGAAGAACAGCCAACGTTGTTACCAATAATTTCTTAGAGTTTGTTCAATTATTGTTT
GTTATACTCTGTTTCCACTTCTTTAGCCAAAATAAGCTCTAAGCAAATTCAAATCTATTTGT
ATAGATGAAGTCTATGAATTTAACATGATAAC

[C/T]

TGAAAAAATGTAAAACTTTGGCTGGGTGTGGTGGCTCACACCTGTAATCCCAGCACTGTG
GGAGGCTGTGGCGGGCGGATCACCTAAGGTCGGGAGCTCCAGACCAGCCTGGCCAACATT
GTGAAACCCCATCTCTACTAAAAATACAAGCATTAGCGAGGCATGGTGGTGGGCACCTGT
AATCCCAGCTACTCAGGAGGCTGAGGCAGGAGAATCGCTTGAACCCAGGAGGCGGAGGT
TGCAGTGAGCCAAGATCGTACCATTGCATTCCAGCCTGGGCAACAAGAGCAAAACTCCGT
CTCAAAAAAAAAAAAAATTAAAACCCAAATAAATTCATGTGGATCTTACCCATATTTCCC
ATGATTTAGATAGGAGTTGGTTTTAAGTTTATTTTTCCACTCAATGGGGGAAAGG

SG12S239

CATCTCTACTAAAAATACAAGCATTAGCGAGGCATGGTGGTGGGCACCTGTAATCCCAGC
TACTCAGGAGGCTGAGGCAGGAGAATCGCTTGAACCCAGGAGGCGGAGGTTGCAGTGAG
CCAAGATCGTACCATTGCATTCCAGCCTGGGCAACAAGAGCAAAACTCCGTCTCAAAAAA
AAAAAAAATTAAAACCCAAATAAATTCATGTGGATCTTACCCATATTTCCCATGATTTAGA
TAGGAGTTGGTTTTAAGTTTATTTTTCCACTCAATGGGGGAAAGGATTTACTAGGAAAATA
ATGTAAACAATCTATTTAAGAAGTCAAATGGCTTTTAAGCACTTAAAAAGCTTTGATATTA
GCAATTTACCCATAAATATTTTGTTAATTACA

[A/T]

AATTTTTTTCTTTTTAGGAAATATTTCTTCTTTTCTTCTTCTTTTGGCTAAGCCTCAGCAGCC
AAATTTTTTATTTTACTTTATTTTAGTTTACTTTTTAGAGACAGGGCCTCCCTCTGTCACAC
ACGCTGGAGTGCAGTGGTATGATCATAGCTCACTATAACCACAAACTCCTGGGCTCAAGC
CATCCTCCCTCCTCAGCCTCCCGAGTAGGTGGGACTACAGGTGTGCACCACTACACCCAGC
TAATTTTTGTAGTTTTTGTAGAGACGGGGTCTTGTCATGTTACCCAGGCTGGCCTCGAACT
CCTGGGCTCAAGCAATCCTCCTTCCTCAGCCTCCCAAAATGCTGGGATTATAGG

SG12S240

TGTGAGATGGCTGGAACCATGGCTGCTATCTTGTGACCATGAGGGGAGGTACCTGGTGGT
TCAAAACTGCCCTGCTAAGTGAGAACGGAATAGGAAGGTTGTAAACAGCCCAAATCTTTC
TTAACCTTGTTAAGCCATTGAGTTGACGAACTTTGCATCTGTCCTGTCTCAGGACTTCTTGT
TAAGCAAGATGGTATATTTTTCATATCGTTTAAATATTTGGCCTTTAAATTTTCAGTAATAG
TCCTTACAGTGATGGCTTTCAGACAGAAAATTAAAAATTTTAAAAAGTGCTATCCTAACTG
ATTCTCTCAATGTATTCAAGTGTAAAGAAATT

FIG. 7.7

[A/T]

CATGTCTAACCTCTCATGGAATTAGAGGGAAAAAATTTCATGTTATTTTAAGTATGTTCAG
TTCTTTTATTAACTCATATTGGTTTCCCCCCTACTCCTTACCCTTGCAACCAAGATAATTTG
CATCTAAGAGGTTTTATTCTGTTTCCACTGATATGTTTAGAAATTACTATATCTGAGGTGG
GTATATTGGGAAAACATACACTACCACTCCTTTGCAGAAATGAGGGCTTATTGCAGCAGC
TACTCGCCCTTGCAATGCTTCCTGCTTGGAAACTCGAAGGACTACATTGAGCAGGTGGA

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AGAGTTTCCCATTCAACAGATTCTTCTATGGAACACAAATTTGCAGTGCCCATTGAAGAAA
CAGAAGTTGCTTTCAAACAGATGTGTTGGTCTCTGTTTTTAGTTTCAGGCTATAAACCTTTT
GAGGGCAGGTACTAACCACCAGGTTAGTACAGTTATGGTGCTTTAGAATCTAATCTCAAG
AGAAAACATCATTTCAAGGTTCATGTTTTTTCAGCCTCCAAATTGGGTGTACATGATCCAC
CTTTAAGGCTTTTTGTTTTTTGCTTTTGTGCCCCTTTATATCTCTTGCAGGAAGACTTGTCTC
TTTCCCTCCACC

[A/G]

CACATTTGTACACAGACTGCCACCTCCACGTTAAAAAAGAAGGCAGGAAGGGGTTGTACT
TGAAGTGACCAGCAAACATTATCTTCAAGCCTTAACCTCTTTTGAAAGATGGTCTTTGCCA
ATAGGGGAGAGACAGTTTCTGGAGGAAACTTCCATGGTGAATACCCAGCCAAAGTAAGCT
TTTTAAAACTGCTCCTGACCCAGAAGGCACATTTCAATATAGGCTGACTAAATGGAGACC
CTCTTTCAGGCCCTAGACTACTTGGCCATTGGCATCCATGAACTTGCTGCAATCAGTG

SG12S438

AAAATAATTAAAAAATTATCCTGGCACAGTAGCATGTGCCTGTAGTCCCAGCTACTCAGG
AGGCTGAGGATCACTTGAGCCCAGGAGTTCAAGGCTGCAGTGAGCTAGGATTGCACCACT
GTGCTCGCTCTAGCCTGGGTTACAGAGACAGGTGTCTAAAAAATAAAAAGAAAAATAGAA
AAGCCCTCTAAGAAGCTTCCGTCTCCGCTGCTCCACTTCCTACCTCTCGAGTTCCTTGTGAC
CCTCCTGTATGCTCTCCTAGCAAATGATTGTTTTCCACTGCACCCCACCCACTTCCCACATC
CTCAAGCACTGAATGTA

[C/G]

TATTACTCAGATTGCCCTGAGCTTGCCTGTCTTCATTTTGCCTACTCCTAGACCGACCCCAA
CACCCAGAACAGAATCCAGCCTCTAGCTGATACTTGAATCTGTGAAATTGACGTAGTAAA
TGGGACCAGCTCTGTCCTTCTCTTACCTTAACTTCCCCTTCCTTCTTTCCTAGAGAGACCTT
AACTTAATGACTCTCTACTTCTTTTCTTTCAAGGGAAGATTGTTCTGCCCATCGCCCCCTCG
GGATTCTGTCTCCATCTAGTAGAGGGAATTTTATAATCCCCTCTTCATTGGTGCT

SG12S460

GAGACCCCATCTCTATTTTAAAAAATAAAAAAAGAAAAGAAAAGAAGAGATTATTAAGA
GTGTGGCTGGTCACCCATTTGATAAGGAGAGTAGTGTGAGTATCAACCATGGACCTAATC
AGCCATCTCAACAGAAGCCAGAAATAGAGTTGGGATTATTCCAGGAGAAATAATGCTTTA
GTCCCCTGCCAGTTGGGACTAAAAGGAAAAGAGAAAACAAGATGGAATGAAGTAAGGCT
GTGAATATGCAAT

[A/C]

CCCTTCAGGAAAAGAGAGGAAGGATCCCAAAGGCAATTCAGACATCATCAGGGCTGCTAC
TCCCACCACAGGCCCAGAGTGGAAAGGCCCCTGGGAACAAGGCTACCTCCATCTTGGTTT
CAAAGAGTGGGACTGCTACTCAGCACTCATGTGGGTGTGGCCCTCACAGACAGCCATGTG
GGCAGTGCTACACTGAGCTGAAGAAGCAGGGACACCCCACTGAAAGATGGGGGTGATAC
CTTCCAGTGGTTCTGGAAGGGAGGACCACCACCCCAGTGGGCCTACAGGGCAGAGCA

FIG. 7.8